ABSTRACT OF THESIS

Name of Candidate DAVID WILLIAM BAYNE

Address [redacted]

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Title of Thesis STUDIES IN THE CHEMISTRY OF ORTHO-NITROBENZENE DERIVATIVES

The scope of the base-catalysed cyclisation reactions of N-cyanomethyl ortho-nitrobenzamides to 1-hydroxyquinazoline-2(1H),4(3H)-diones has been investigated and the reaction has been shown to be a viable synthetic route to these relatively inaccessible heterocycles.

N-Cyanobenzyl 3,5-dinitrobenzamides have been shown to cyclise to 5,7-dinitrophthalimidines under mildly basic conditions - a process which involves the formal displacement of hydride ion. Under similar conditions N-cyanobenzyl 3-nitrobenzamides give rise to a mixture of the isomeric 5-nitro and 7-nitrophthalimidines, again by formal displacement of hydride ion. Nitrophthalimidines have also been synthesised by cyclisation of the related N-cyanobenzyl 2-chloro-3,5-dinitro- and 2-chloro-5-nitrobenzamides with displacement of chloride ion. Attempted base-catalysed cyclisations of related ortho-nitrophenylhydrazides and α-cyanobenzyl 2-chloro-3,5-dinitrobenzoate were unsuccessful.

A novel 3-hydroxyquinoline synthesis is described. Thus, the potassium hydroxide catalysed cyclisation of 2-nitrobenzoylacetylacetone in ethanol affords 2-acetyl-3-hydroxyquinoline in excellent yield. The structure of this product has been established by spectroscopic methods and by chemical transformations.

An efficient synthesis of 1,1-disubstituted 2-(2-nitrophenyl)ethylene oxides, by the sodium hypochlorite oxidation of the corresponding 2-nitrobenzylidene derivatives, has been developed. The hydrogen chloride catalysed reactions of these disubstituted epoxides have shown a greater degree of participation by the nitro-group than has been observed previously in the case of the monosubstituted 2-(2-nitrophenyl) ethylene oxides. Depending on the nature of the substituents, the products resulting from such participation are 6-chloro-1,3-dihydroxy-2-phenylquinolin-4(1H)-one or compounds tentatively assigned anthranil structures.

An attempt to demonstrate analogous participation of the nitro-group in the hydrogen chloride catalysed reaction of 1-benzoyl-2-(2-nitrophenyl) cyclopropane resulted only in the isolation of a hydrogen chloride adduct formed by rupture of the cyclopropane ring and addition of hydrogen chloride.

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STUDIES IN THE CHEMISTRY OF ORTHO-NITROBENZENE DERIVATIVES

by

David William Bayne B.Sc.

Thesis presented for the degree of Doctor of Philosophy

University of Edinburgh 1974

DECLARATION

I declare that this thesis is my own composition, that the work of which it is a record has been carried out by myself and that it has not been submitted in any previous application for a Higher Degree.

The thesis describes the results of research carried out in the Department of Chemistry, University of Edinburgh under the supervision of Dr. G. Tennant between October 1969 and September 1972.

[redacted]

ACKNOWLEDGEMENTS

I would like to express my appreciation and thanks to my supervisor, Dr. G. Tennant, for his guidance and encouragement throughout the course of this work.

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I am grateful to Dr. J.N. Done who carried out the high speed liquid chromatographic separation and Mrs. D.W. Williams for her care and patience in typing the thesis.

SUMMARY

The scope of the base-catalysed cyclisation reactions of N-cyanomethyl ortho-nitrobenzamides to 1-hydroxyquinazoline-2(1H),4(3H)-diones has been investigated and the reaction has been shown to be a viable synthetic route to these relatively inaccessible heterocycles.

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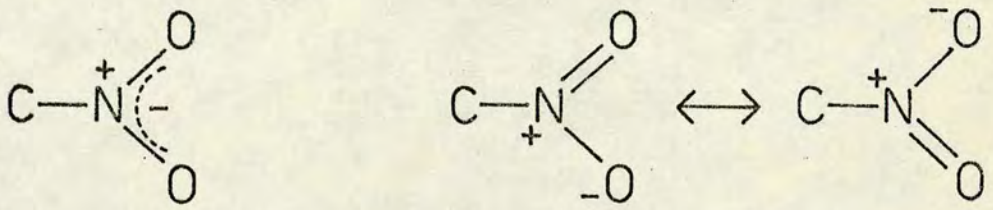
CONTENTS

Chapter One

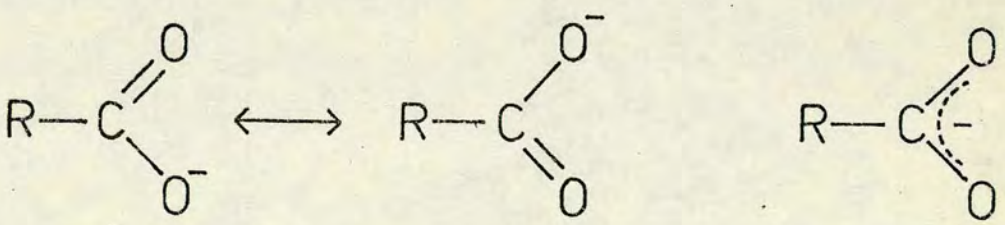
A Survey of Nitro group-Side chain Interactions in 2-Substituted Nitrobenzene Derivatives

The nitro-group can accurately be represented by structure (1). However formula (2) is a more convenient depiction for the purposes of this thesis. This formula is not intended to imply any difference in the oxidation states of the two oxygen atoms or in the nitrogen to oxygen bond lengths.



(1) (2) (3)

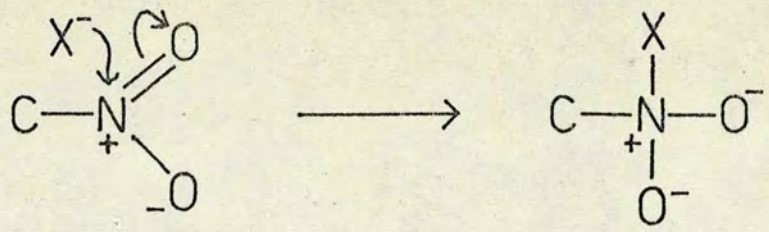
The nitro-group can be considered as a resonance hybrid of two equally contributing forms (2) and (3), or in terms of delocalisation of π-electrons over nitrogen and oxygen as in structure (1). This situation is comparable to that present in the carboxylate anion which can be considered as a resonance hybrid of (4) and (5) or as the delocalised structure (6).



(4) (5) (6)

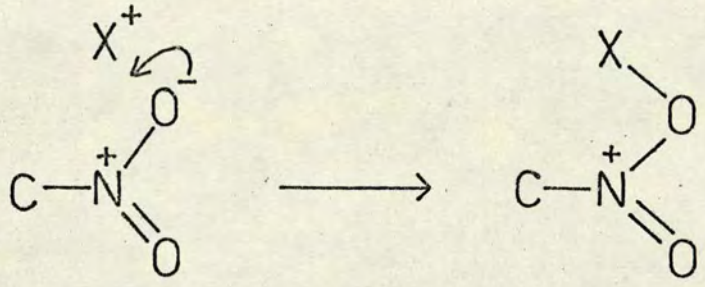
Because of its dipolar nature, the nitro-group ought to undergo reactions of two types,

(a) those in which the nitro-group suffers nucleophilic attack at nitrogen [(7) → (8)].



(7) (8)

(b) those in which the nitro-group undergoes electrophilic attack at oxygen [(9) → (10)].



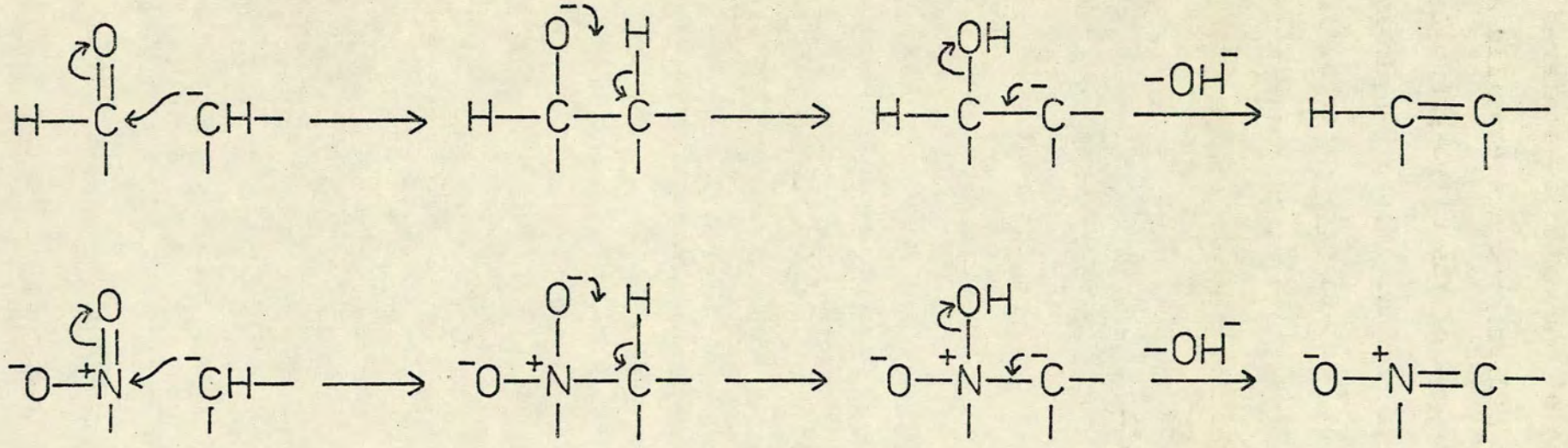
(9) (10)

Neither mode of reaction is observed intermolecularly, except in a few cases involving organometallic reagents,[1] because the required steric relationship for interaction between the nitro-group and the attacking species is not achieved. Nitrobenzenes substituted in the ortho- position overcome the steric difficulty since the nitro-group and side-chain are held in close proximity and reaction can occur if the ortho-side-chain has the necessary nucleophilic or electrophilic character.

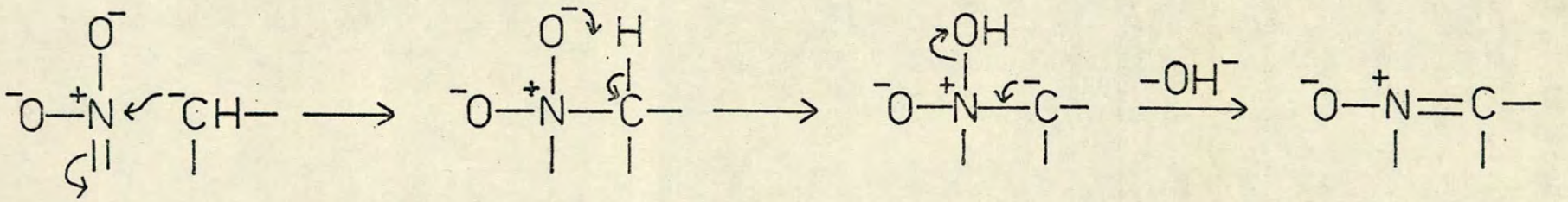
Reactions of ortho-Nitrobenzene Derivatives involving Intramolecular Nucleophilic Attack at Nitrogen

(a) by Carbon Nucleophiles

These reactions can be considered mechanistically as being analogous to an intramolecular aldol addition



Scheme 1

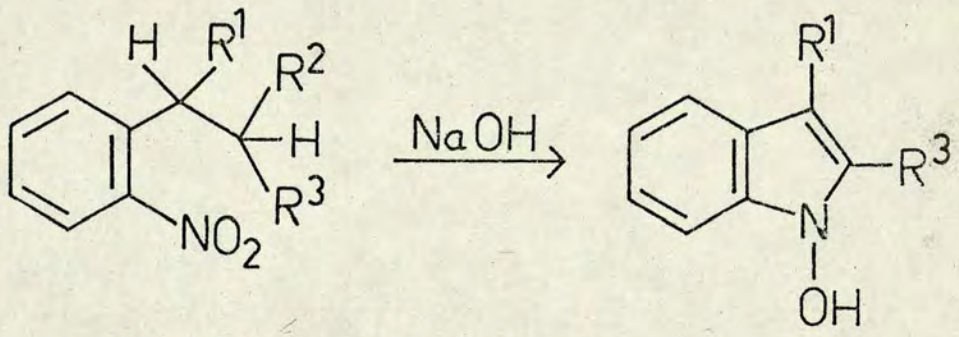


Scheme 2

(Scheme 1). The production of the anion is achieved by the use of a basic reaction medium, and nucleophilic attack by the carbanion on the nitrogen of the nitro-group leads to the formation of an N-oxide or tautomeric N-hydroxy heterocycle. In the case of certain ortho-nitrobenzene derivatives, attack by the side-chain carbanion may involve the aci-nitro tautomer of the nitro-group (Scheme 2).

Formation of N-hydroxyindoles

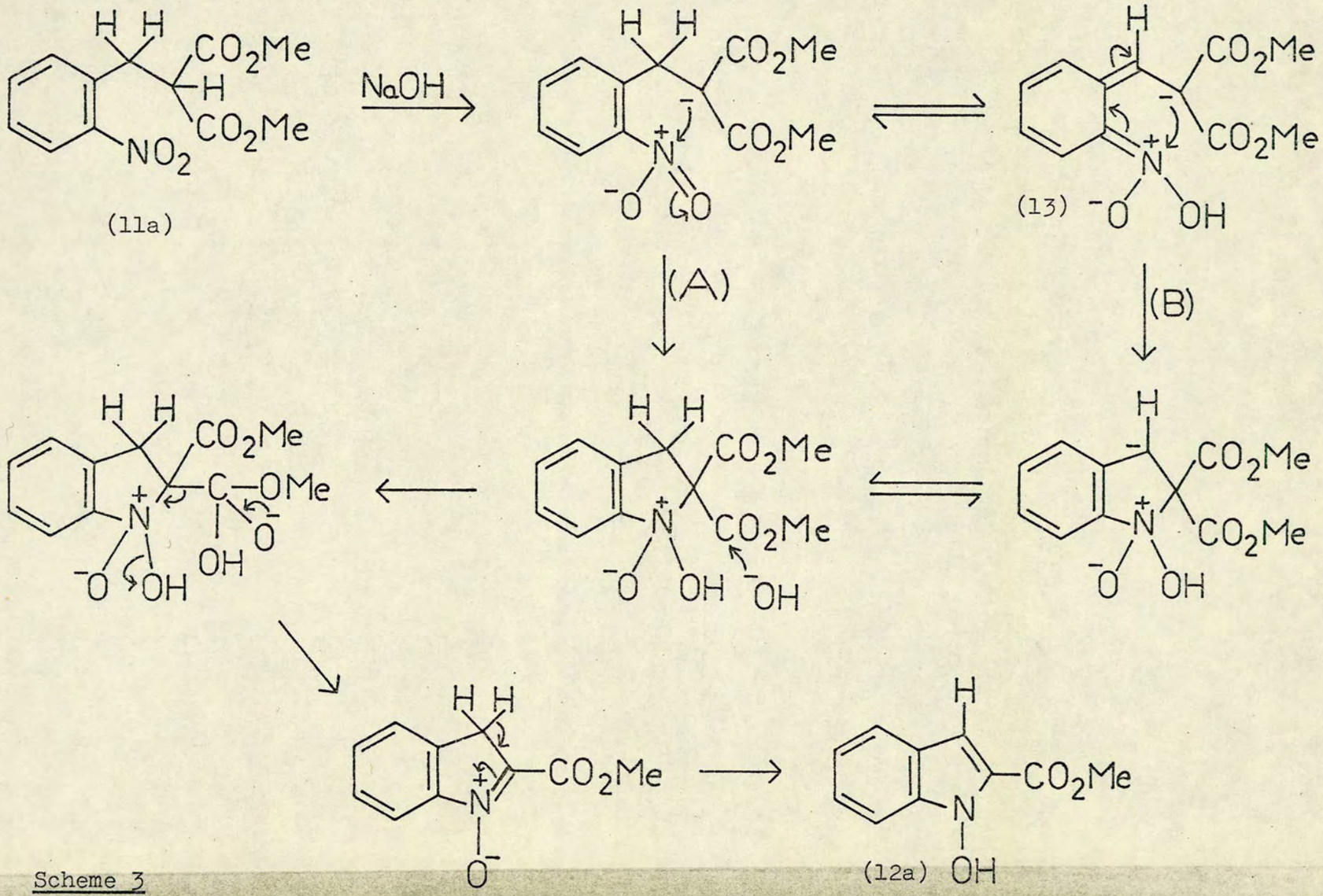
The base-catalysed cyclisation of a variety of ortho-nitrobenzyl compounds (11) is perhaps the most general method for synthesising N-hydroxyindole derivatives (12)[2-5]



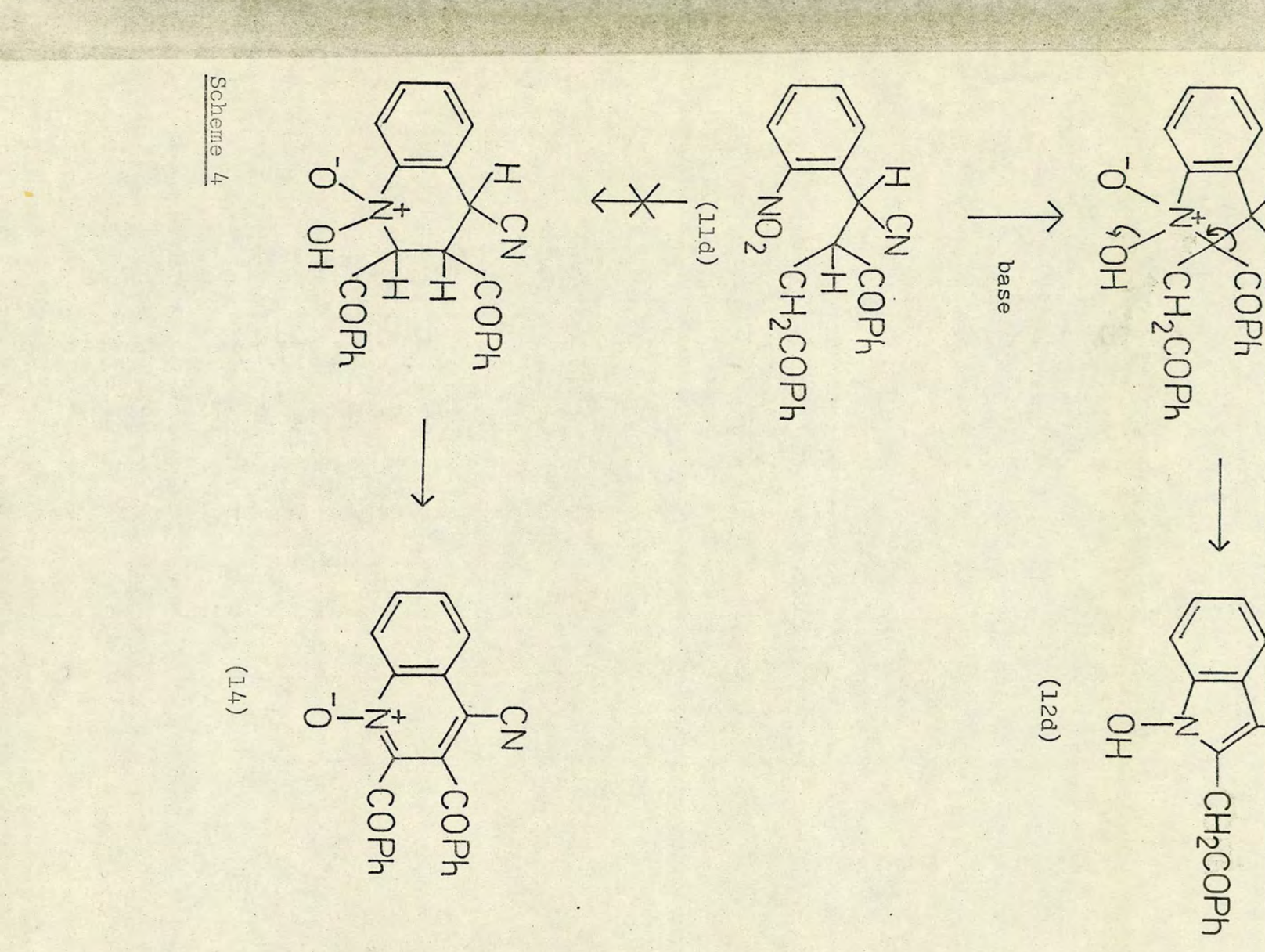
(11) (12)

	R^1	R^2	R^3
a;	H	CO_2Me	CO_2Me
b;	H	COMe	CO_2Et
c;	CN	CO_2Et	CO_2Et
d;	CN	COPh	CH_2COPh

The list of ortho-nitrobenzyl derivatives (11) which undergo this type of cyclisation, though by no means exhaustive, demonstrates the scope of the reaction and provides an insight into the mechanism involved. Thus the transformation [(11a) ⟶ (12a)] (Scheme 3) is catalysed by sodium hydroxide



Scheme 3

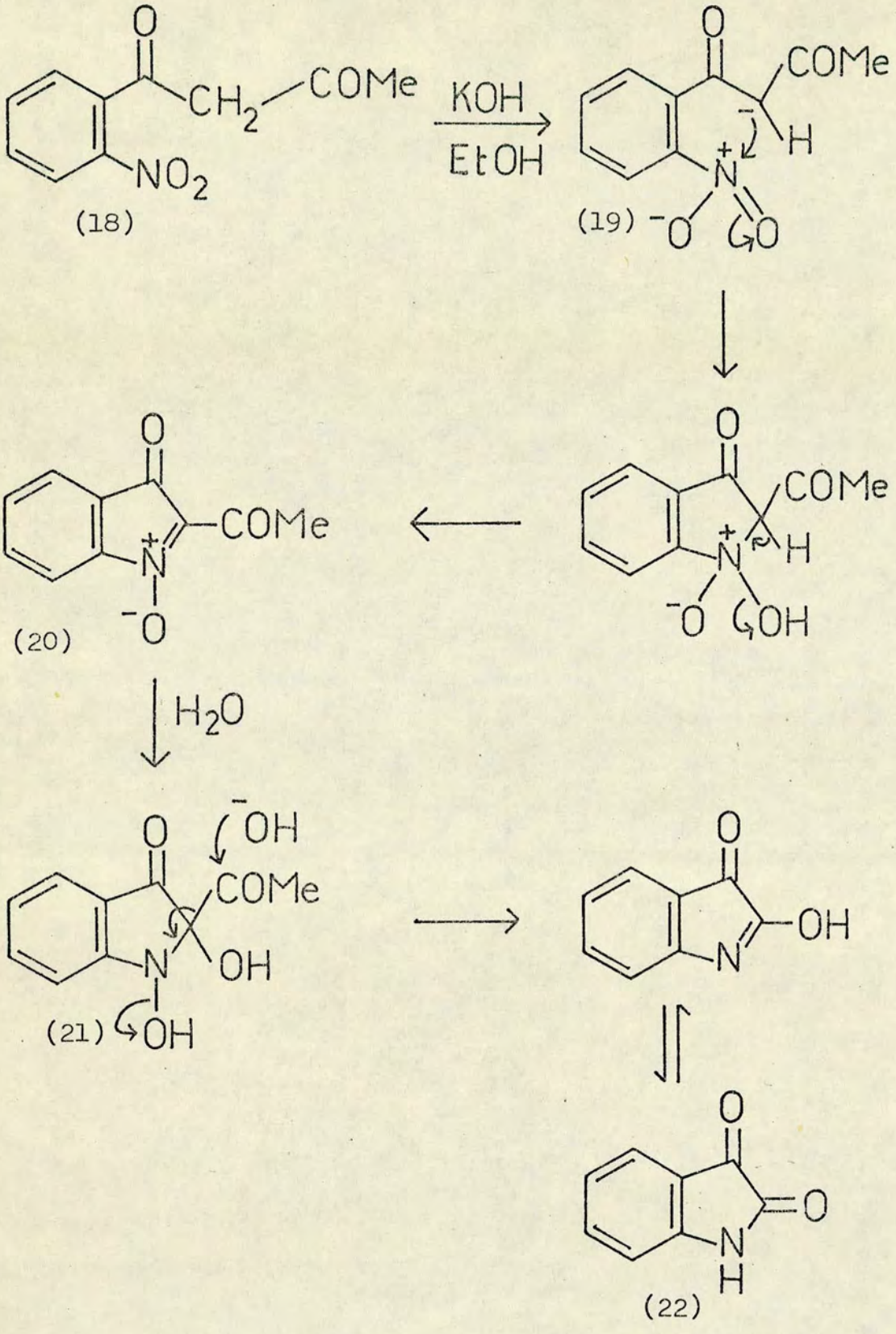


Scheme 4

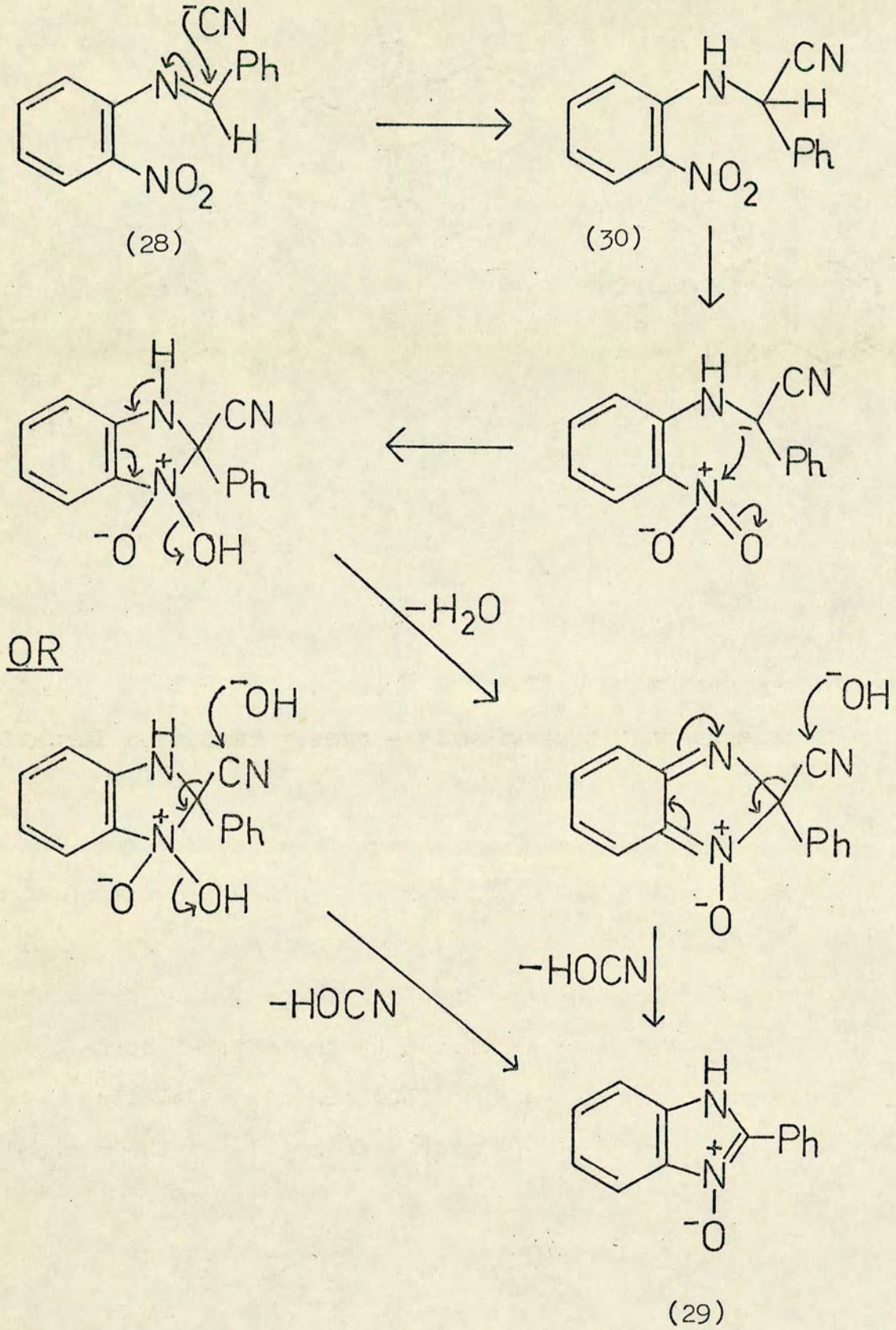
and yields 2-methoxycarbonyl-1-hydroxyindole (12a).[2] As is general with this mode of cyclisation, the side-chain must contain an acidic β-hydrogen to permit formation of a carbanion suitably placed to effect ring formation. In the present case this is provided for by the presence of one or two electron-withdrawing groups on the β-carbon atom in the side-chain. If the precursor has two acidic centres or if a strongly basic cyclising agent is used there is the complication of quinoline formation. Since these ortho-nitrobenzyl substrates can tautomerise to the aci-nitro structures (13), this cyclisation may involve attack by the carbanion either on the intact nitro-group [step (A)] or on the modified nitro-group [step (B)]. At this stage it is not possible to predict which mechanism is operating but the formation of quinolines in these reactions is more easily rationalised (see later) by mechanism (A).

An interesting feature of the indole synthesis [(11) → (12)] is demonstrated by the cyclisation of (11d) which in principle could give rise either to an indole derivative (12d) or a quinoline derivative (14). In practice[5] the 1-hydroxyindole (12d) (Scheme 4) is the sole product demonstrating the preference for the formation of the five-membered product.

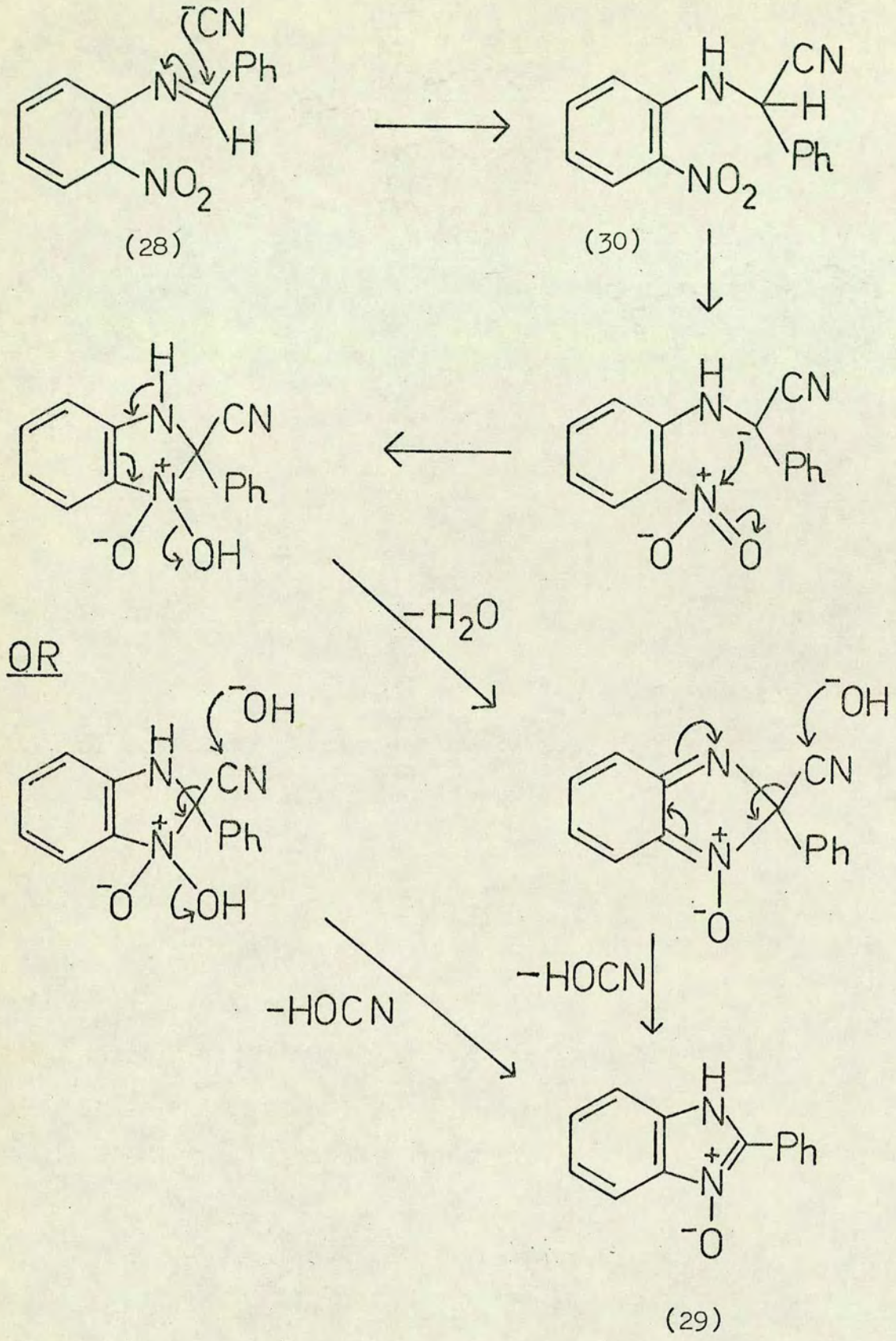
1-Hydroxyindole derivatives (17) are available in one step from 2-nitrobenzylidene derivatives (15) by reaction with ethanolic potassium cyanide.[4,5] The reaction presumably involves formation of the hydrogen cyanide adduct (16) and subsequent cyclisation as indicated (Scheme 5).



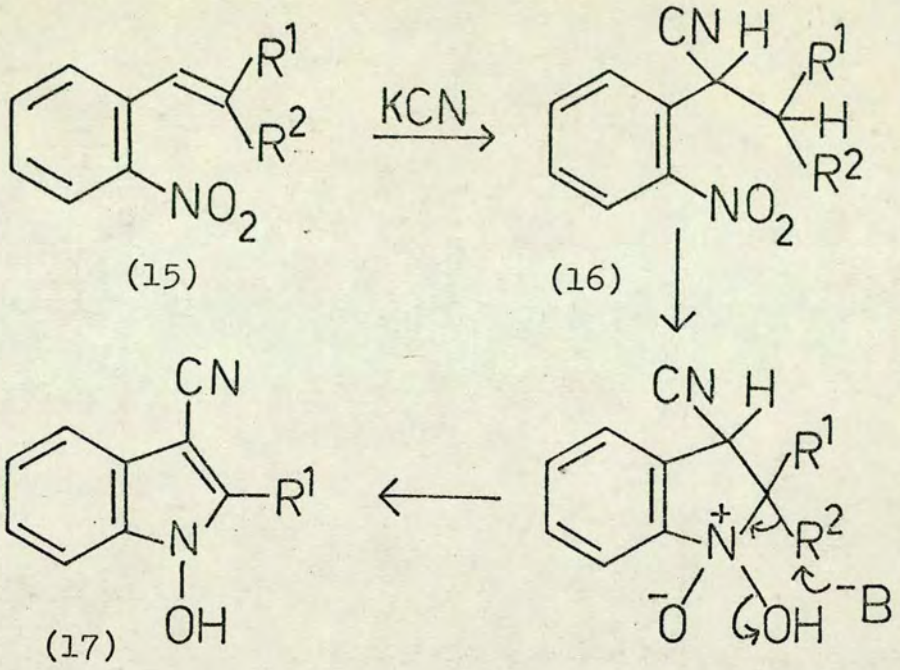
Scheme 6



Scheme 7



Scheme 7



	R^1	R^2
a;	CO_2Et	CO_2Et
b;	Me	COPh
c;	COPh	H

Scheme 5

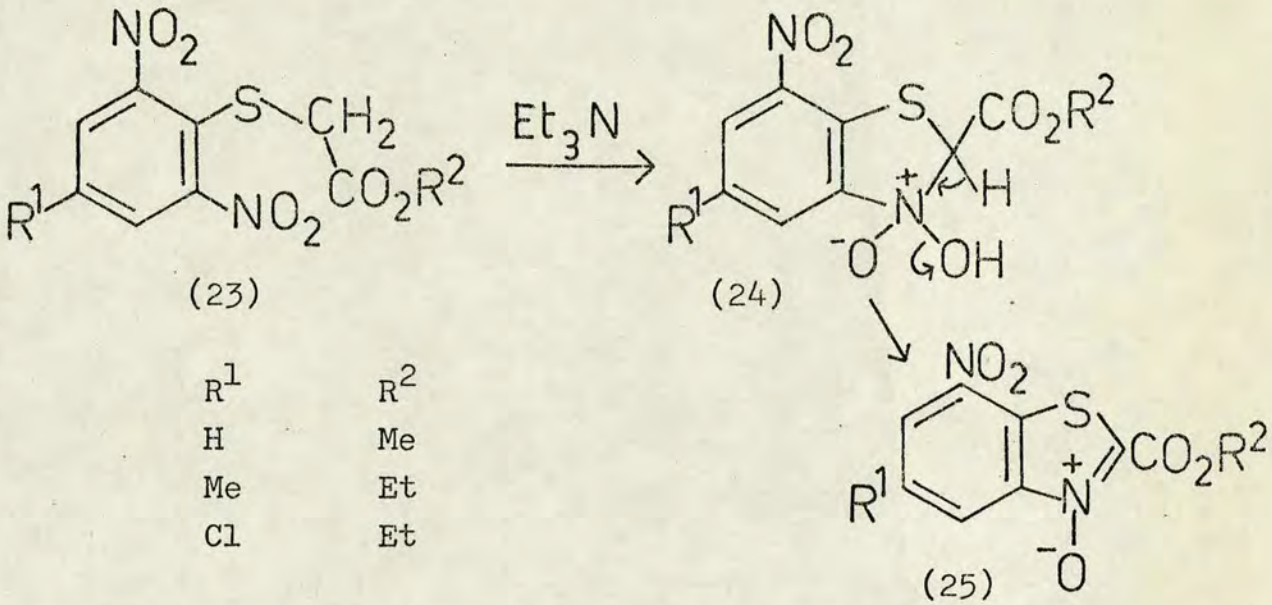
Formation of Isatins

There being no benzylic hydrogen, 2-nitrobenzoyl derivatives cannot cyclise via the aci-nitro tautomer and so ring formation must occur by carbanion attack on the unmodified nitro-group. Cyclisations of this type leading to five-membered rings are rare but one probable example of this process is the conversion of 2-nitrobenzoylacetone (18) by reaction with ethanolic potassium hydroxide into isatin (22).[6] The mechanism of this interesting transformation has not been established, but may involve the initial formation and subsequent decomposition of 2-acetylisatogen (20) (Scheme 6). Thus, attack by the stabilised carbanion (19) on the nitro-group produces, by aldol-type condensation,

the isatogen (20). Isatin formation is then readily explained by hydroxide attack on the hydrated form (21) of the isatogen (20), [(20) → (21) → (22)]. However, more clear-cut cases of the aldol-type cyclisation of ortho-nitrobenzoyl derivatives are exemplified by processes leading to N-oxygenated quinazolinones to be described later.

Formation of Thiazole N-Oxides

The base catalysed cyclisation of 2-nitrophenylthio-acetic esters (23) provides a simple route to thiazole N-oxides (25).[7] A probable mechanism is aldol-type

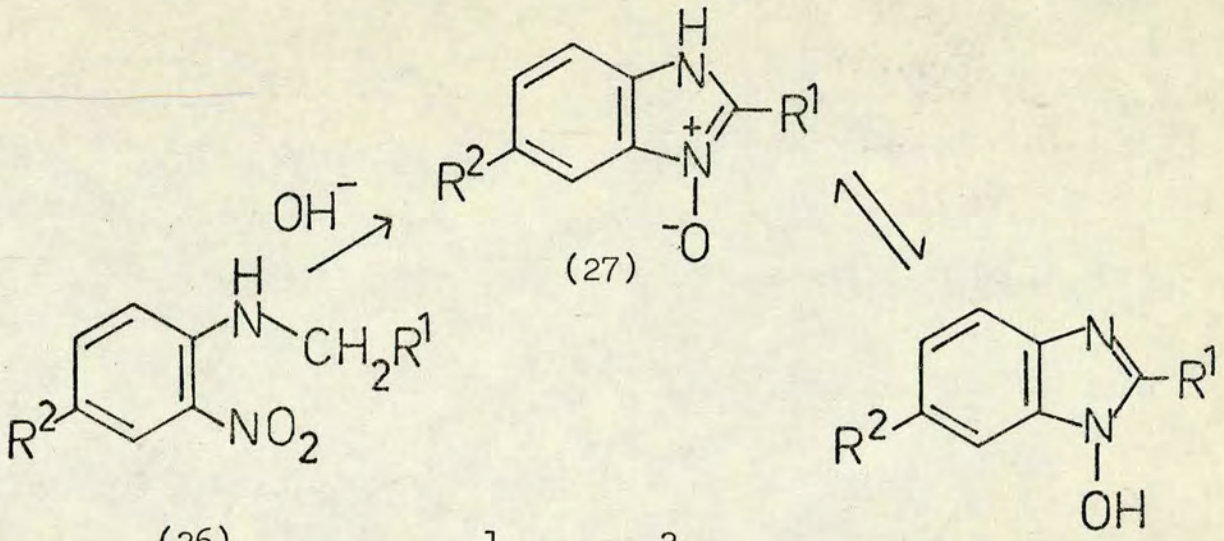


R^1	R^2
H	Me
Me	Et
Cl	Et

addition to the intact nitro-group to form the intermediate (24) followed by dehydration to afford the thiazole N-oxides (25).

Formation of Benzimidazole N-Oxides

An important route to benzimidazole N-oxides (27) involves the cyclisation, under basic conditions, of N-substituted 2-nitroanilines (26) containing an active methylene group.[6,8,9,10] The mechanism of these cyclisations

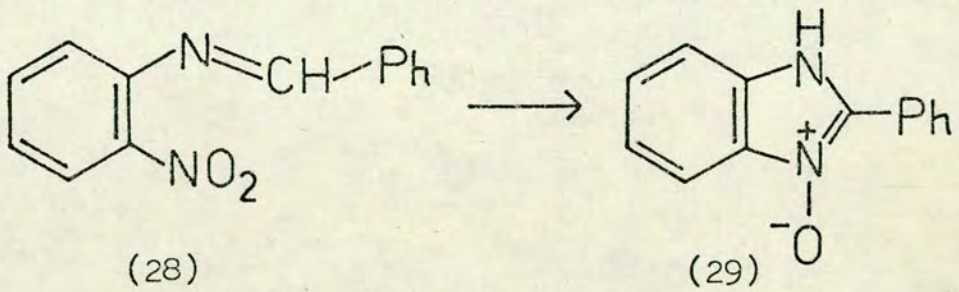


(26) (27)

R^1	R^2
PhCO	Me
Ph	H
CO_2Me	NO_2
$CONHCH_2CO_2H$	NO_2

would appear to be similar to that involved in the indole synthesis described previously - namely carbanion formation then ring closure by internal aldol addition followed by dehydration.

A similar reaction[11] involving milder conditions is the cyclisation of the anil (28) by methanolic potassium cyanide to 2-phenylbenzimidazole-N-oxide (29). This transformation can be explained by the initial formation of a hydrogen cyanide adduct (30) and its aldol-type cyclisation to give the product (Scheme 7). The mechanism

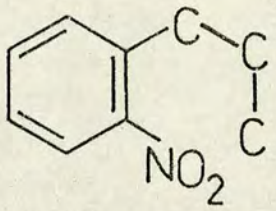


(28) (29)

for the concomitant loss of the cyano group involved in this cyclisation is not clear but may occur as indicated in Scheme 7 .

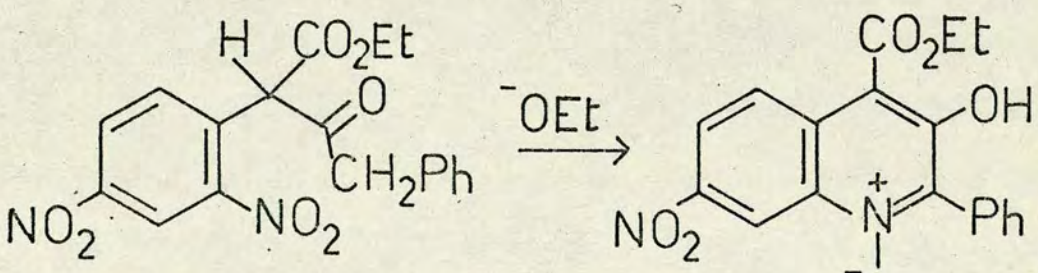
Formation of N-Oxygenated Quinolines

The formation of a quinoline nucleus by base-catalysed cyclisation of an ortho-nitrobenzene derivative necessitates a precursor having a carbon skeleton of the type (31). The



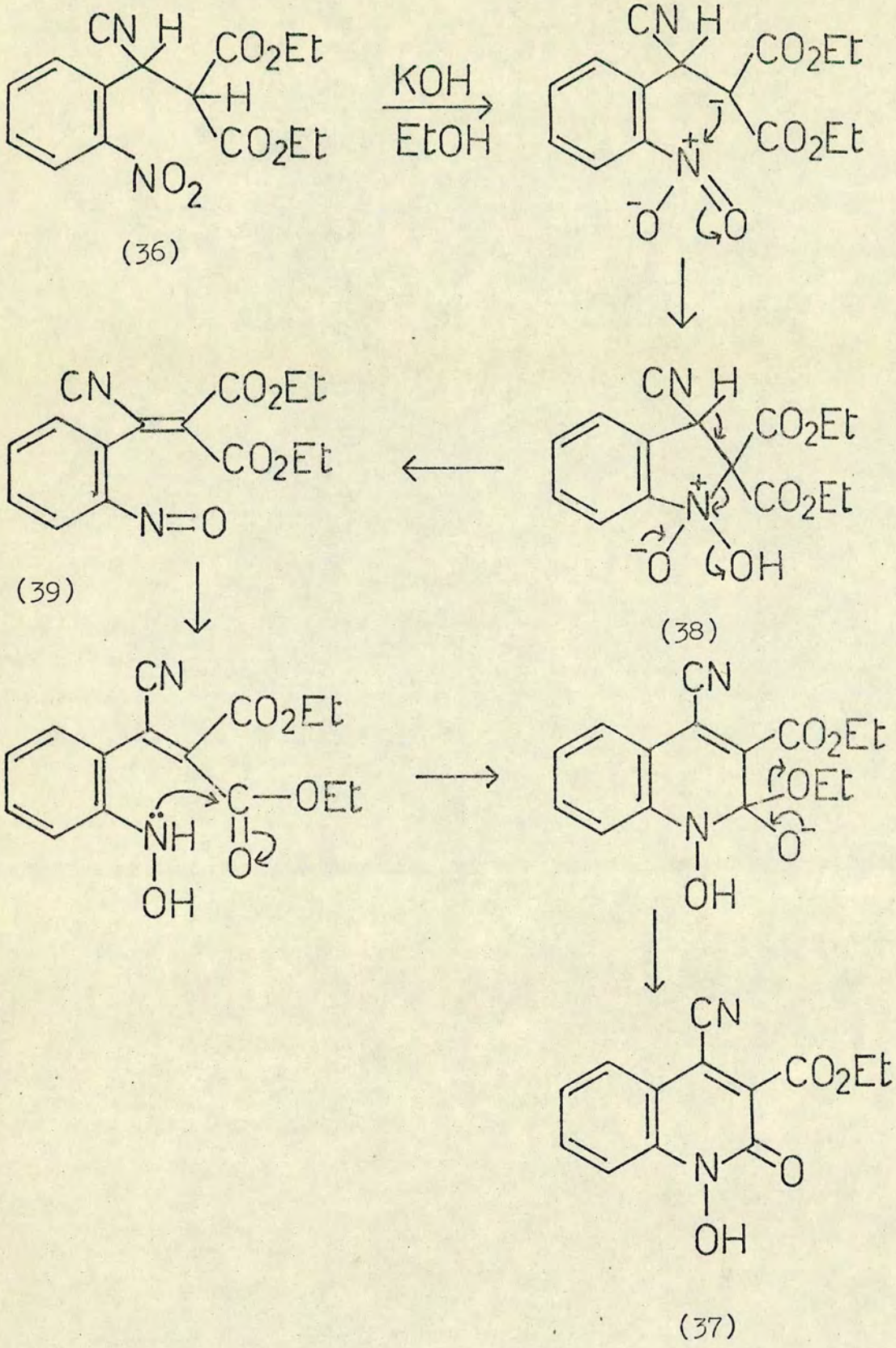
(31)

terminal carbon of the side-chain must bear a moderately acidic hydrogen in order to permit carbanion formation and subsequent cyclodehydration. Such a simple intramolecular aldol-type process operates in the base-catalysed formation of the quinoline N-oxide (33) from the keto-ester (32).[12,13]

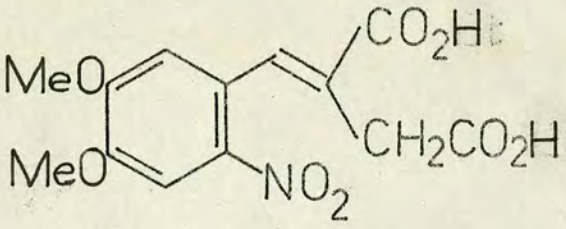


(32) (33)

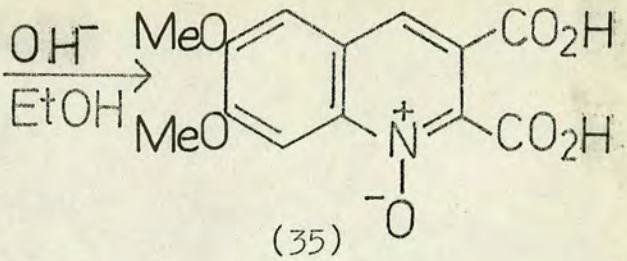
A similar type of cyclisation is involved in the base-catalysed cyclisation of 2-nitroveratrylidenesuccinic acid (34) to the N-oxide (35).[14]


CN H
CO2Et
H
CO2Et
NO2
KOH
EtOH
(36)
CN H
CO2Et
CO2Et
N+
O
O
CN H
CO2Et
CO2Et
N+
O
OH
(38)
CN
CO2Et
CO2Et
N=O
(39)
CN
CO2Et
C—OEt
O
NH
OH
CN
CO2Et
OEt
O
N
OH
CN
CO2Et
O
N
OH
(37)

Scheme 8

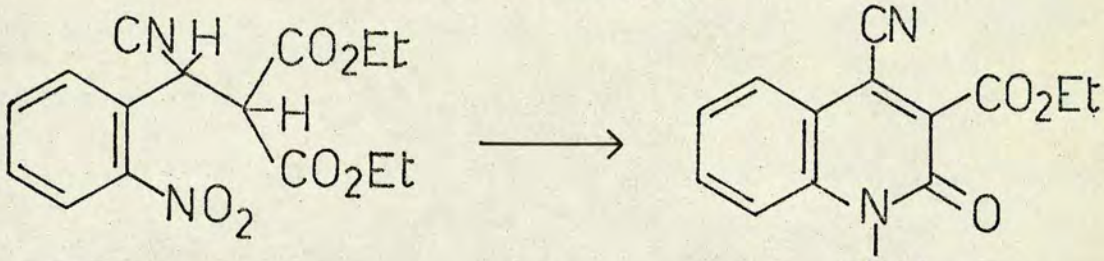


(34)



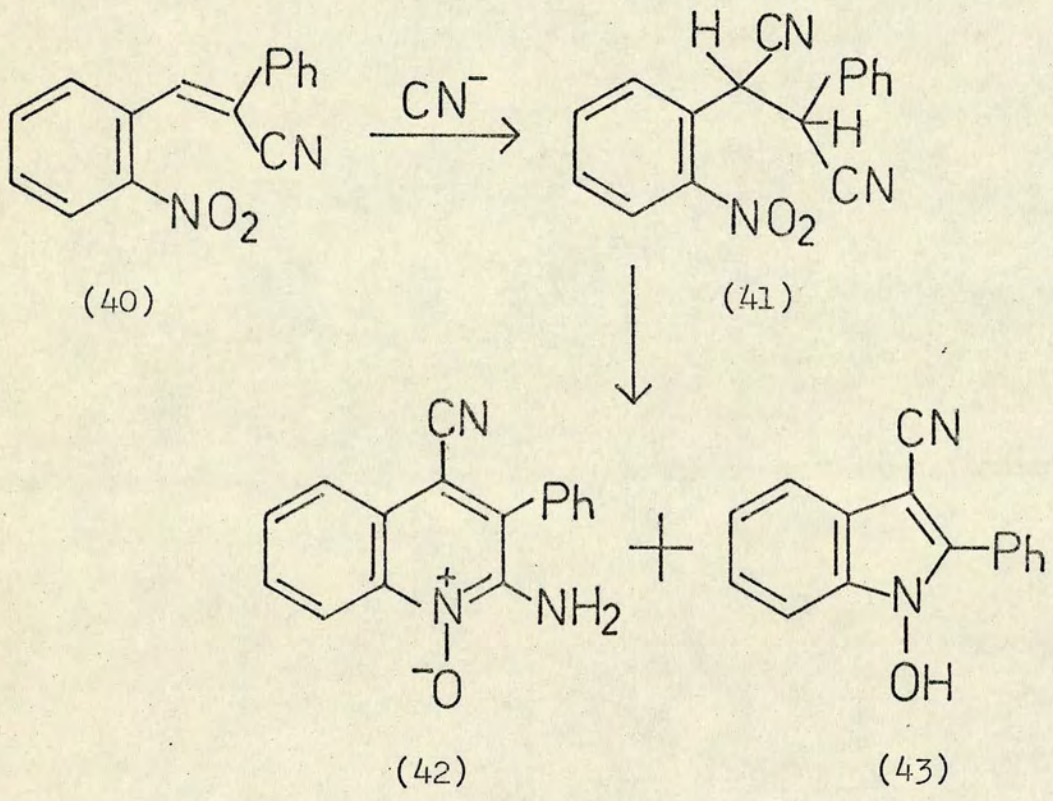
(35)

In contrast to their cyclisation in weakly basic media to 1-hydroxyindoles (cf. page 4 and Scheme 3) ortho-nitrobenzyl derivatives of the type (36) are converted by treatment with ethanolic potassium hydroxide into N-hydroxy-carbostyril derivatives such as (37).[4]



(36) (37)

Reactions of this type can again be explained in terms of a course (Scheme 8) initiated by nucleophilic attack on the ortho-nitro-group by a carbanion generated in the side-chain. Ring-opening of the initial adduct (38) to the nitroso intermediate (39) and subsequent reductive cyclisation in the alcoholic alkaline medium[15] accounts for the formation of the cyclic hydroxamic acid (37). The corresponding aci-nitro mechanism (cf. Scheme 3, page 4) does not explain the controlling effect of base strength on the course of these reactions. Thus, indole formation is observed when only the hydrogen on the β-carbon has marked acidity and



(40) (41) (42) (43)

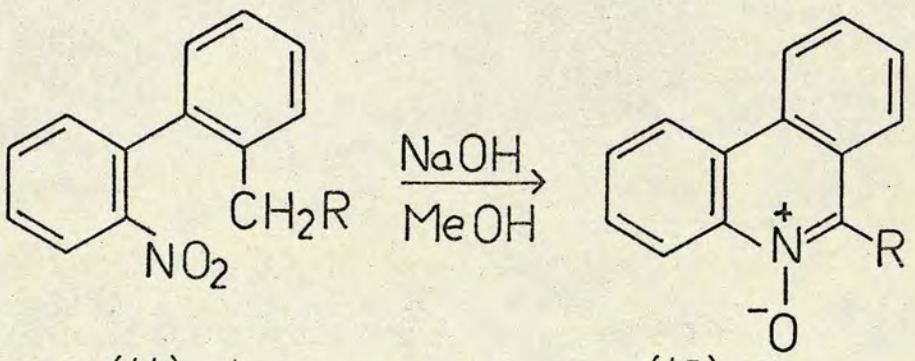
Scheme 9

when a weakly basic medium is used. On the other hand, where the acidity of the α-hydrogen is enhanced and using a strongly basic catalyst, quinoline formation predominates.

These contentions are supported by the fact that where the acidity of α- and β-hydrogen atoms in the side-chain is finely balanced, roughly equal amounts of indole and quinoline products result. Thus the treatment[16] of the hydrogen cyanide adduct (41) [produced *in situ* from the benzylidene derivative (40)] with ethanolic potassium cyanide affords a roughly 50:50 mixture of the quinoline N-oxide (42) and the N-hydroxyindole (43) (Scheme 9).

Formation of Phenanthridine N-Oxides

The base-catalysed cyclisation of 2'-substituted-2-nitrobiphenyls (44) to phenanthridine N-oxides (45)[17,18] offers the best evidence for the simple intramolecular aldol-type process. These reactions are formally analogous



(44) (45)

[R = CO_2Me, CN]

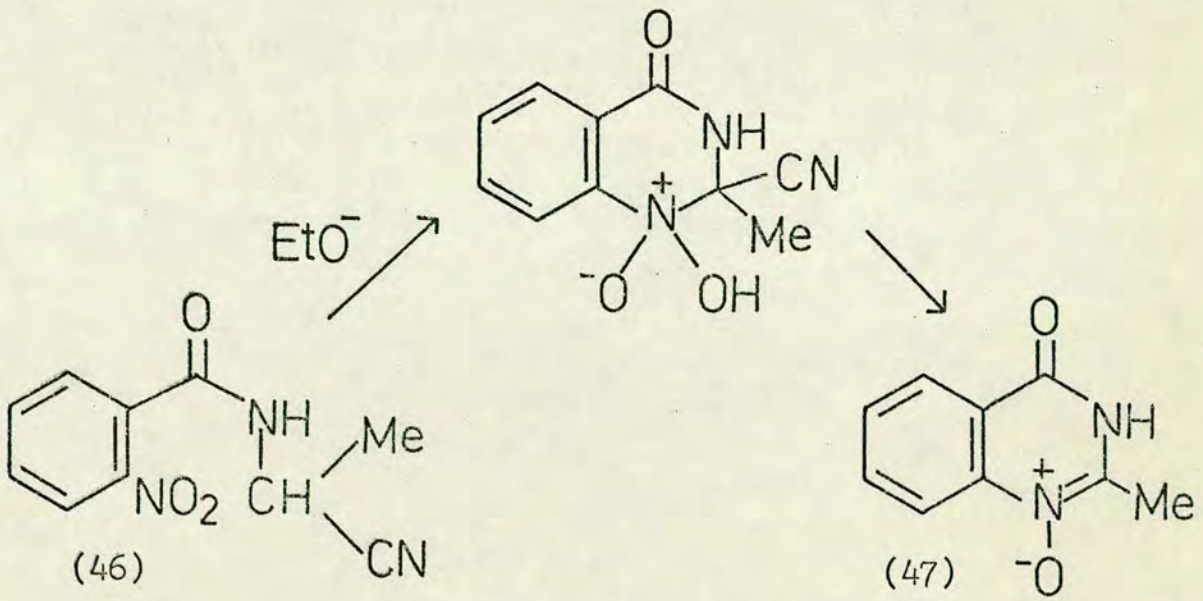
to the *ortho*-nitrobenzylidene succinate cyclisation (cf. page 8) and are successful only when R in (44) is electron-withdrawing.[17,18] The ease with which these

cyclisations [(44) → (45)] are effected must be due at least in part to the favourable steric situation, the carbanion generated in the side-chain being held in close proximity to the nitro-group.

Formation of Quinazoline N-Oxides

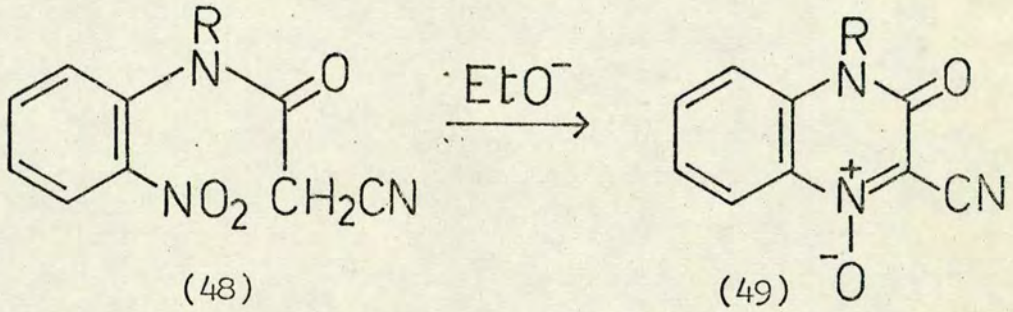
In the majority of reactions already discussed, cyclisation could occur either by direct interaction across space between the carbanion centre in the side-chain and the intact nitro-group, or alternatively interaction could occur after isomerisation of the nitro-group to the aci-nitro tautomer. However this ambiguity of mechanism does not apply in the base-catalysed cyclisation of ortho-nitrobenzamide derivatives to quinazoline N-oxides.

This type of transformation is exemplified by the reaction of 2-nitrobenzoylaminoacetonitrile (46) with ethanolic sodium ethoxide to afford 2-methylquinazolin-4(3H)-one 1-N-oxide (47)[19] in moderate yield. This cyclisation cannot involve an aci-nitro intermediate and requires the loss of the cyano-group presumably in a similar fashion to that discussed in the formation benzimidazole derivatives (cf. page 7 and Scheme 7).



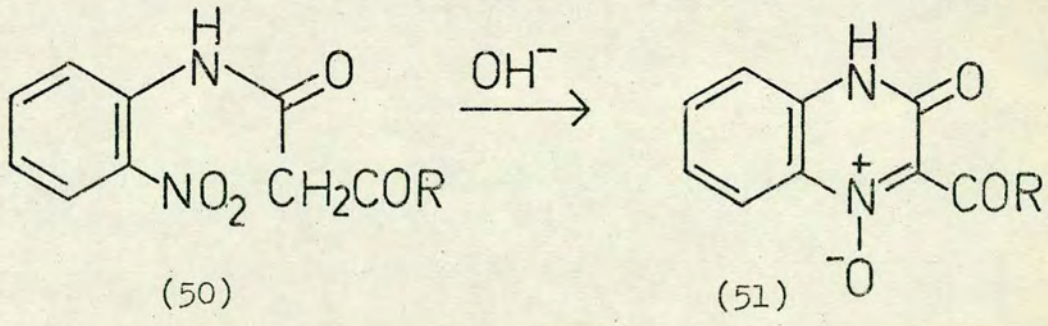
Formation of Quinoxaline N-oxides

The widest application of the base-catalysed intramolecular aldol-type condensation of ortho-nitrobenzene derivatives to the synthesis of any one class of compound is probably represented by the cyclisation of ortho-nitroacetanilide derivatives to quinoxalin -2(1H)-one 4-N-oxides. Thus, 3-cyanoquinoxalin-2(1H)-one 4-N-oxides (49) are the products of the cyclisation of α-cyano-2-nitroacetanilides (48) under a variety of basic conditions.[20]



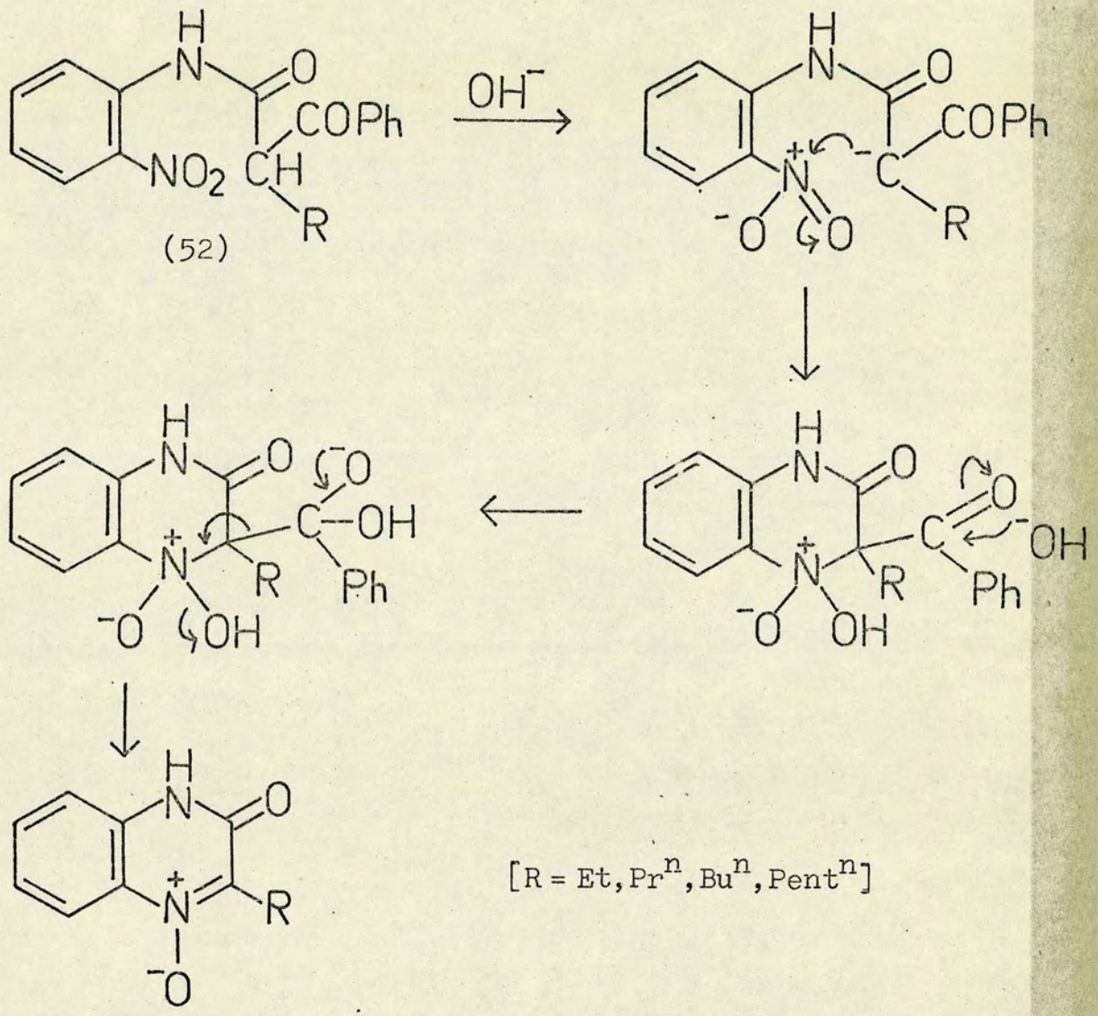
(48) (49)

In an analogous manner 3-acylquinoxalin-2(1H)-one 4-N-oxides (51) are formed from ortho-nitroacetanilide derivatives (50)[20,21] in which the methylene group is activated by acyl substituents.



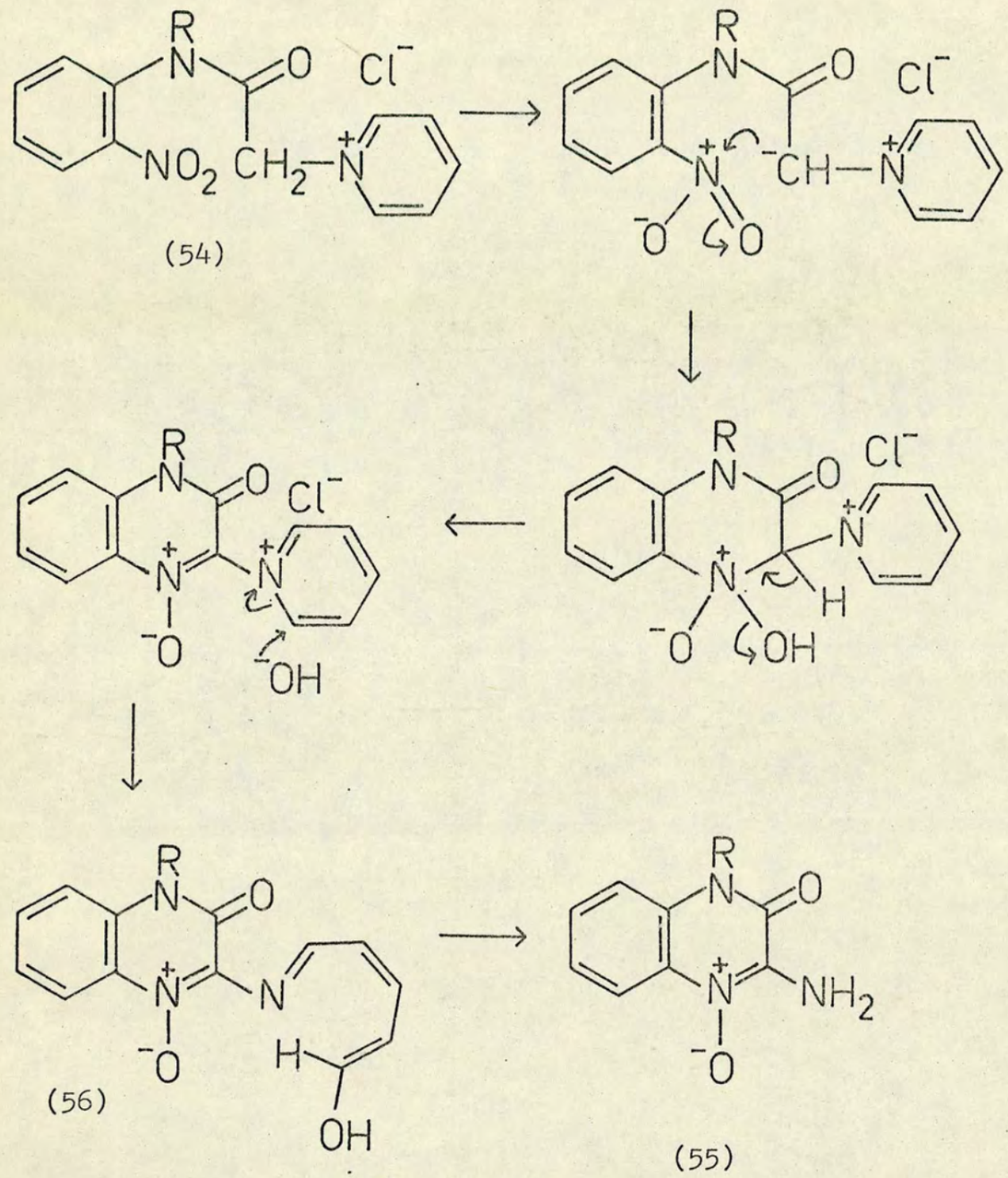
(50) (51)

[R = Me, Ph, OEt]



[R = Et, Pr^n, Bu^n, $Pent^n$]

Scheme 10

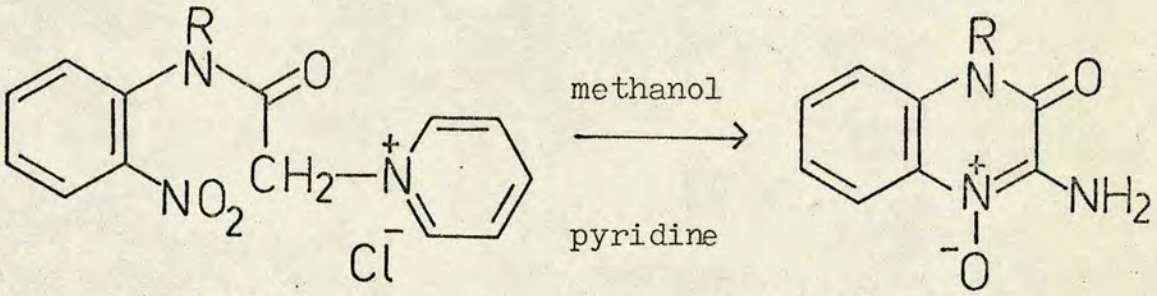


[R = H, Me]

Scheme 11

3-Alkylquinoxalin-2(1H)-one 4-N-oxides (53) cannot be obtained by direct cyclisation of α-alkyl-2-nitroacetanilides (50, R for COR) since the methylene hydrogen atoms are not sufficiently activated to permit carbanion formation in the side-chain. They are, however, available in good yield by the conversion [(52) → (53)][22] (Scheme 10) in which activation is provided by a benzoyl group which is subsequently lost in the aromatisation step of the cyclisation.

Pyridinium salts of the type (54) undergo base-catalysed cyclisation to 3-aminoquinoxalin-2(1H)-one 4-N-oxides (55),[21,22] the importance of this reaction being that



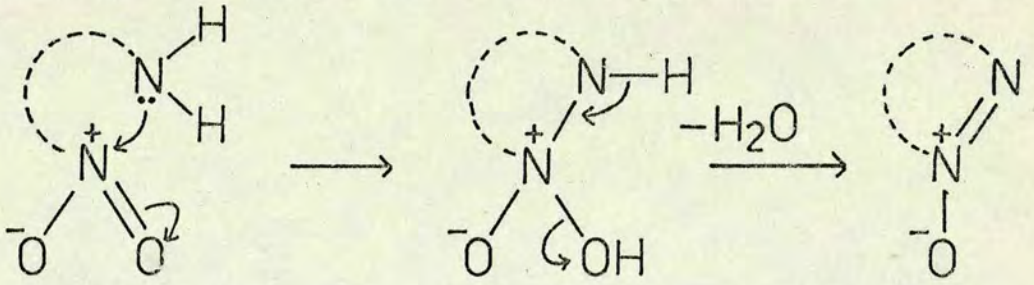
(54) (55)

the product (55) cannot be obtained by direct cyclisation due to the deactivating effect of the amino-group on the methylene group. As there is evidence[23] that the transformation [(54) → (55)] involves the intermediate formation of an anil (56) a possible mechanism is suggested in Scheme 11.

(b) by Nitrogen Nucleophiles

Intramolecular attack by nitrogen nucleophiles on aromatic nitro-groups can also be formulated as aldol-type condensations which in their simplest form lead ultimately to azoxy products [(57) → (58) → (59)]. In cyclisations

of this type the nitro-group condenses with a neutral nitrogen atom bearing a lone pair of electrons. Clearly the

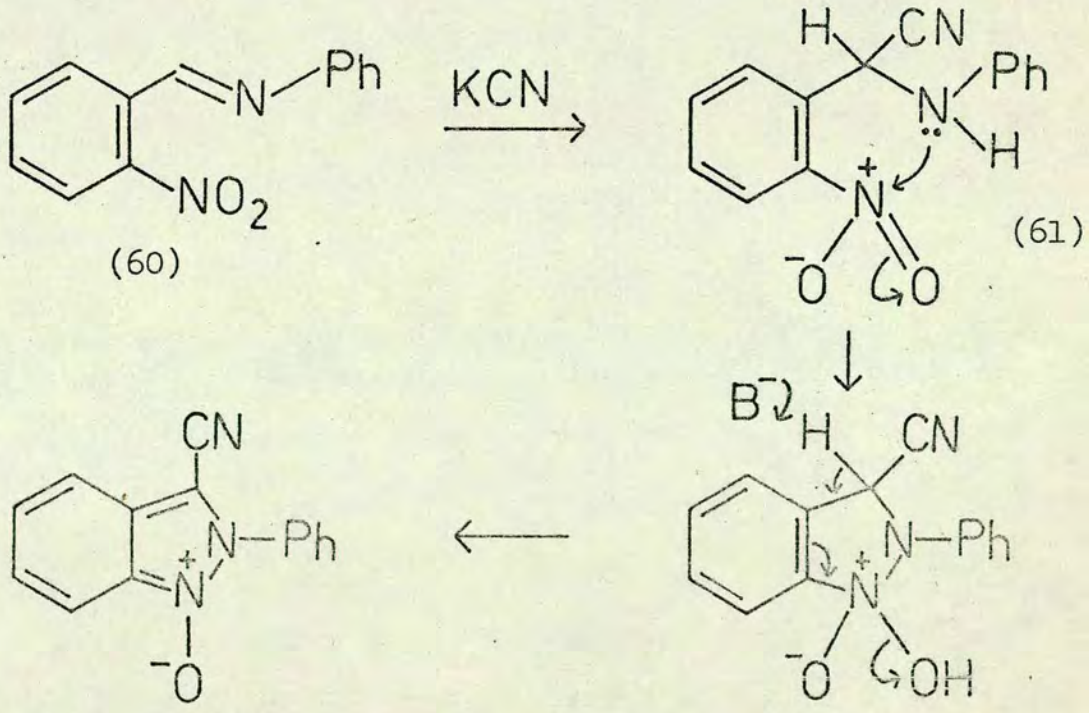


(57) (58) (59)

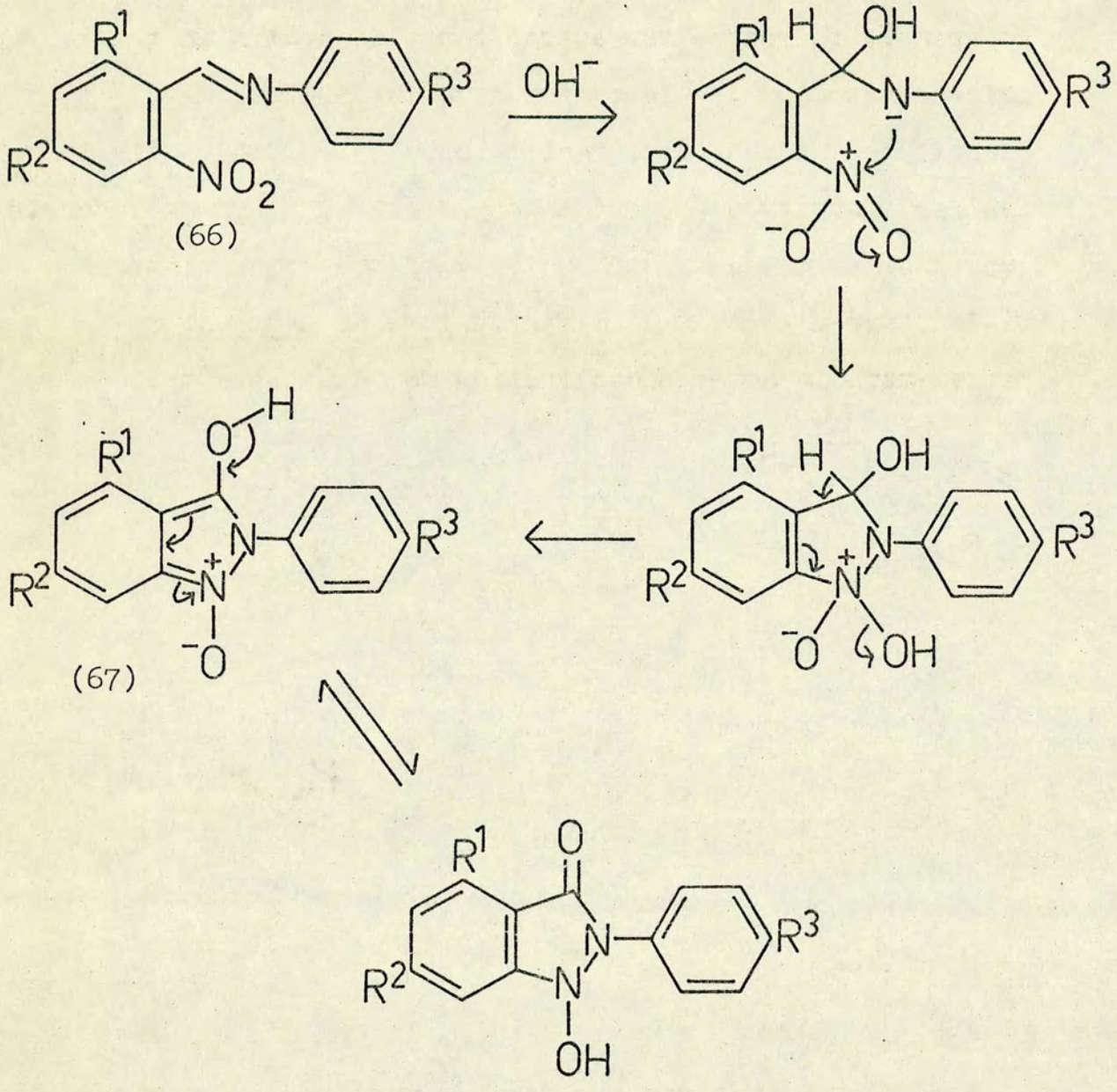
main criterion for the success of such a reaction is the provision of a moderately basic nitrogen centre. However, as will be discussed later even a weakly basic amidic centre can sometimes participate in such cyclisations.

Formation of Indazole N-Oxides

When the Schiff base (60), formed by reaction of 2-nitrobenzaldehyde with aniline, is treated with aqueous potassium cyanide the first product is the hydrogen cyanide adduct (61)[24] which can be isolated. However further treatment with mild base converts the adduct (61) into 3-cyano-2-phenylindazole 1-oxide (63).[24]



(60) (61) (62) (63)



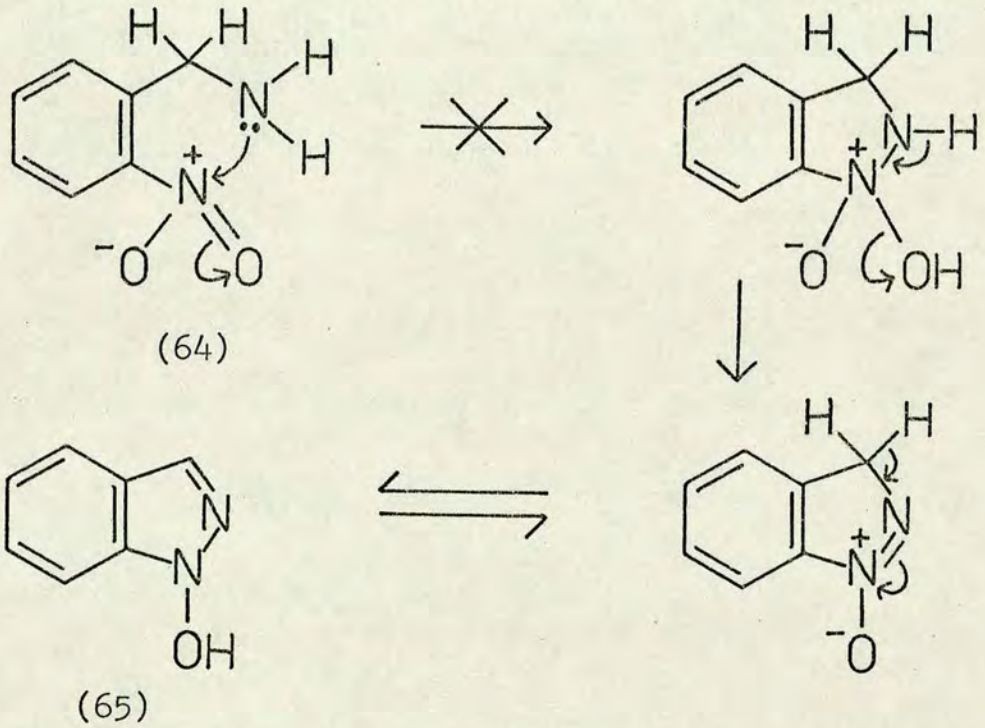
(66)

(67)

R^1	R^2	R^3	Yield(%)
H	H	H	0
H	NO_2	H	16
NO_2	NO_2	H	50
NO_2	NO_2	Me	83

Scheme 12

The function of the base in this cyclisation is apparently to remove the acidic benzylic proton in the intermediate (62). In contrast to the similarly constituted adduct (61), 2-nitrobenzylamine (64) fails to cyclise[25] under basic conditions to afford N-hydroxyindazole (65) despite the enhanced basicity of the amino-centre in (64) compared with (61). The failure of ortho-nitrobenzylamine to undergo cyclisation can thus be attributed

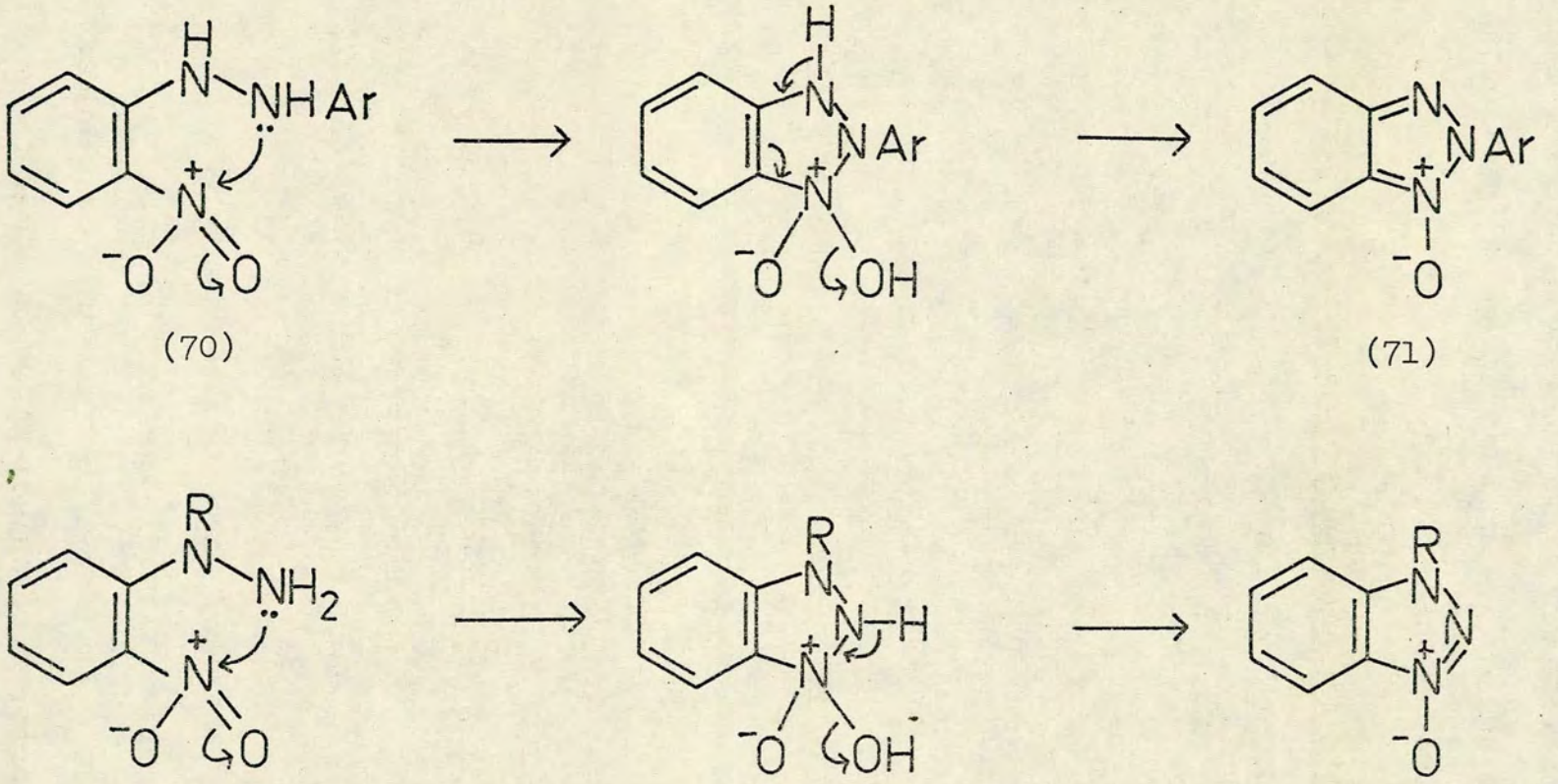


(64)

(65)

to the absence of a mobile benzylic hydrogen as in the adduct (62).

The operation of activating and deactivating effects in these indazole N-oxide cyclisations is strikingly illustrated in the formation of 3-hydroxyindazole N-oxides (67)[26] when ortho-nitrobenzylidene anils (66) are heated with ethanolic sodium carbonate (Scheme 12). As already stated cyclisations of this type are promoted by enhanced basicity in the amino-centre. Another factor is the

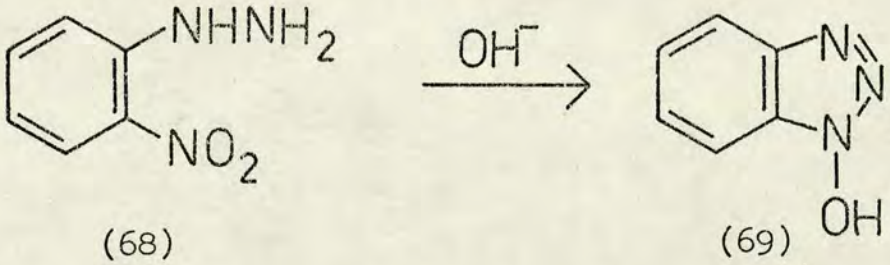


Scheme 13

electron deficiency of the nitro-group. These factors are demonstrated by the steady increase in the yield of cyclic product observed (See Scheme 12) by the introduction of electron-withdrawing nitro-groups into the benzylidene nucleus and by the incorporation of the electron rich methyl group in the aniline ring.

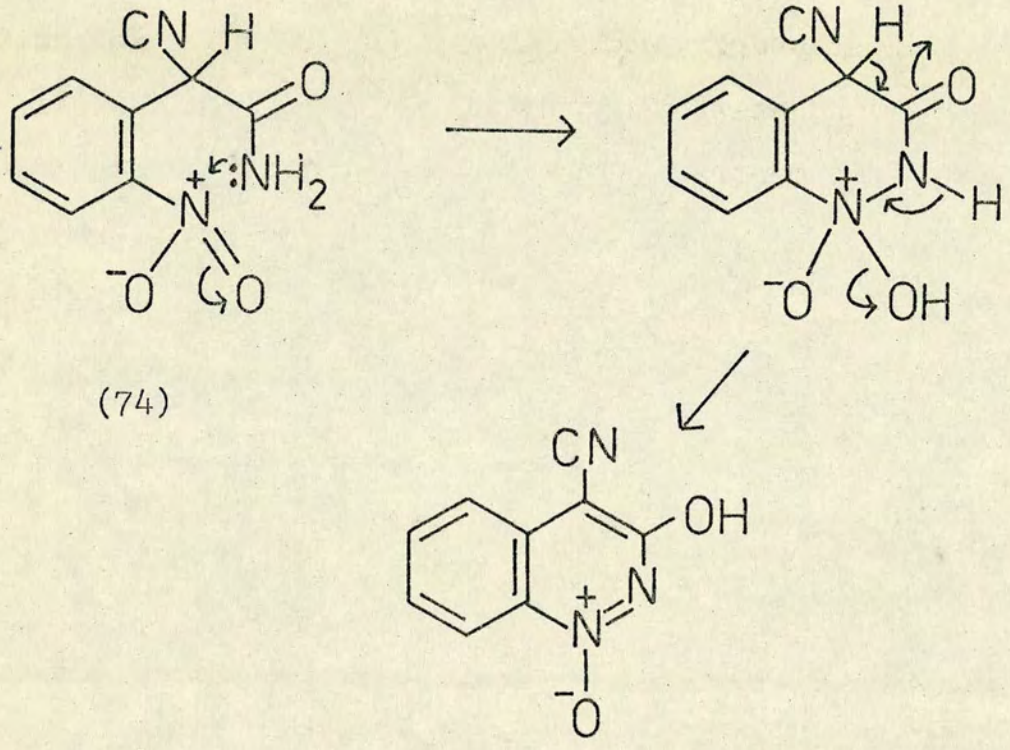
Formation of N-Oxygenated Benzotriazoles

One of the first reactions involving the interaction of an aromatic nitro-group with an ortho-side-chain to be reported was the conversion[27] of 2-nitrophenylhydrazine (68) by treatment with alkali into the sodium salt of 1-hydroxybenzotriazole (69). This cyclisation is of general



(68) (69)

applicability[28] to ortho-nitrophenylhydrazine derivatives including N,N-disubstituted structures as exemplified by the alkali or acetic acid cyclisation of 2-nitrohydrazobenzenes (70) to 2-substituted benzotriazole 1-N-oxides (71),[29,30] and the similar transformation [(72) → (73)] of the isomeric hydrazines (72)[31] (Scheme 13). Again the simple nature of these cyclisations provides strong evidence for the operation of the 'across-space' aldol-type of process. However as noted before, mechanisms involving rearrangement to an aci-nitro tautomer prior to cyclisation are equally possible.



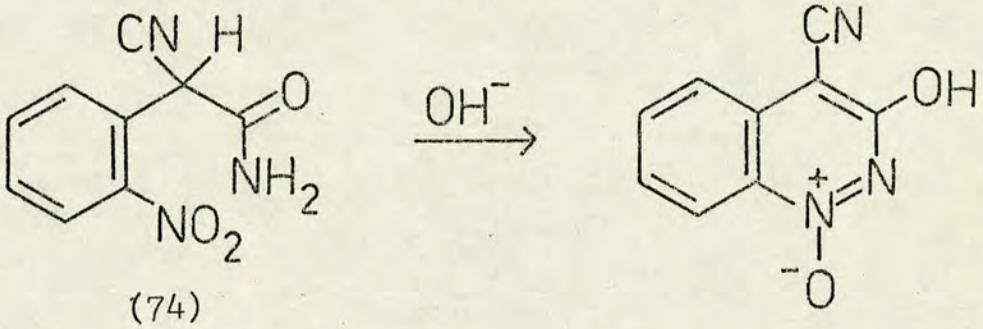
(74)

(75)

Scheme 14

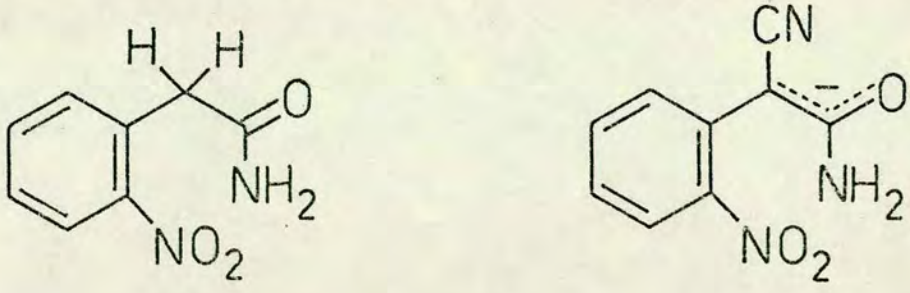
Formation of Cinnoline N-Oxides

The cyclisations leading to N-oxygenated indazoles and benzotriazoles discussed before exemplify the operation of the aldol process for side-chains involving a fairly basic amino-centre. On the other hand the sodium hydroxide catalysed cyclisation of 2-nitrophenylcyanoacetamide (74) to 4-cyano-3-hydroxycinnoline N-oxide (75)[32] involves the apparent condensation of the nitro-group with a weakly basic amidic centre. The internal aldol-type mechanism

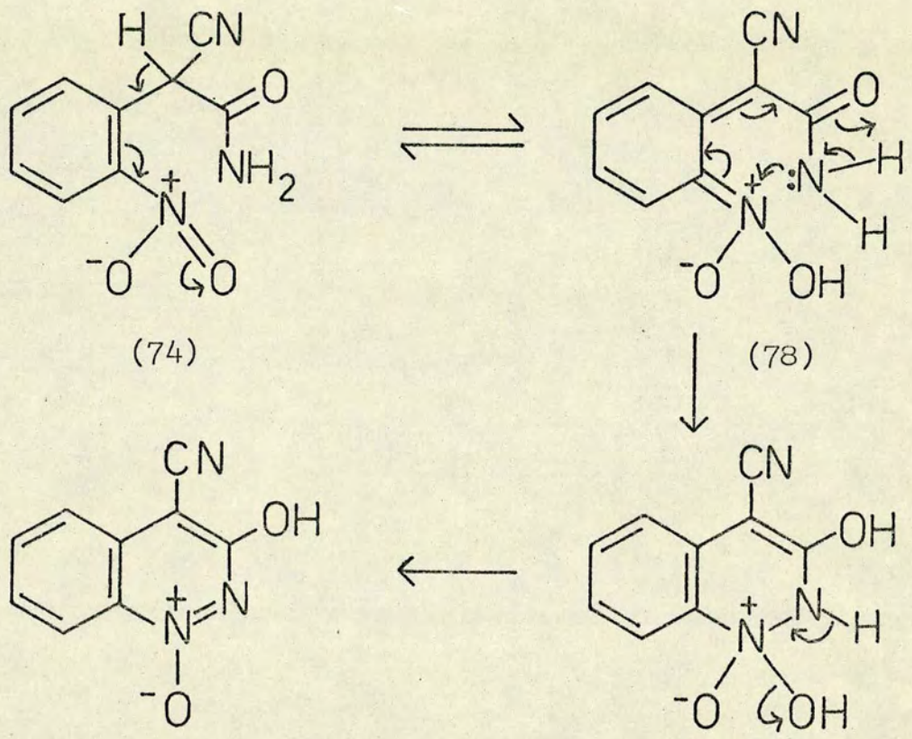


(74) (75)

(Scheme 14) can be formulated for this reaction. However the failure[18] of 2-nitrophenylacetamide (76) to undergo cyclisation under similar conditions and the weakly basic character of the amido-group make this mechanism doubtful and indicate that a prerequisite for successful cyclisation is the presence of an acidic benzylic hydrogen. This

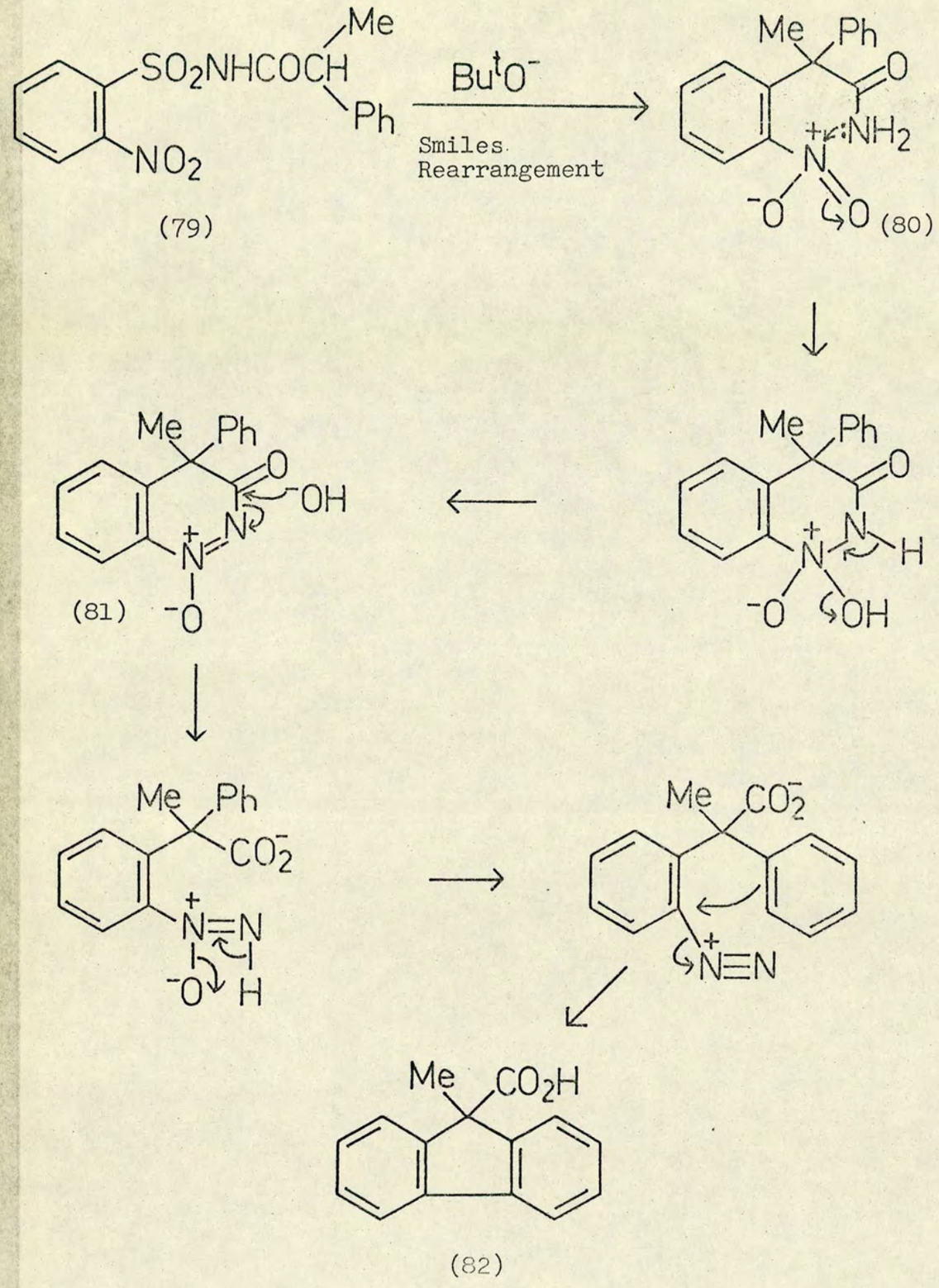


(76) (77)



(74) (78) (75)

Scheme 15



(79) (80) (81) (82)

Scheme 16

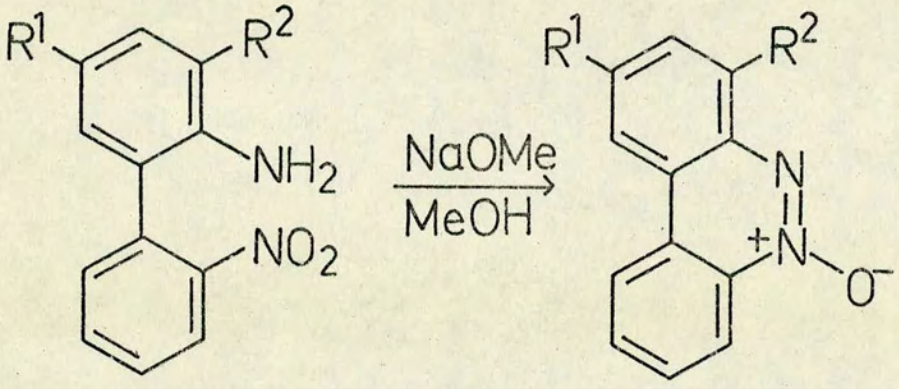
requirement can be interpreted in terms of enhancement of the nucleophilicity of the amido-group by virtue of preferential enolisation involving the benzylic centre [cf. (77)]. Competing enolisation to the benzylic centre will be much less in 2-nitrophenylacetamide.

Alternatively a mechanism (Scheme 15) involving prior rearrangement to an aci-nitro intermediate (78) can be invoked.

A cinnoline N-oxide (81) is suggested[33] as an intermediate in the base-catalysed rearrangement of the sulphonamide (79) to the fluorene carboxylic acid (82) (see Scheme 16). There being no benzylic hydrogen in (80), neither enolisation nor rearrangement to the aci-nitro tautomer is possible. This suggests the amido-group is sufficiently basic to allow cyclisation to the cinnoline N-oxide (81), which being unable to achieve stabilisation by aromatisation undergoes ring-opening by base attack. Rearrangement and loss of nitrogen then account for the formation of the fluorene carboxylic acid (82) (Scheme 16).

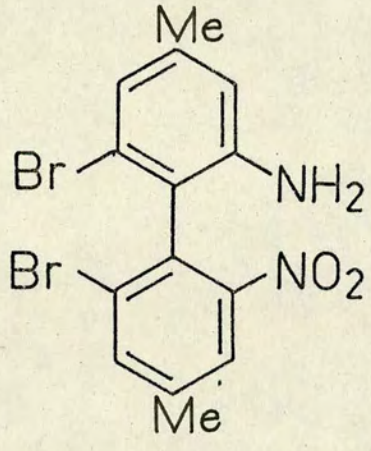
Formation of Benzocinnoline N-Oxides

In reactions which have features in common with both the cyclisations leading to phenanthridine N-oxides (cf. page 10) and the cinnoline N-oxide type, aminonitrobiphenyls (83) undergo base-catalysed cyclisation to benzo[c]cinnoline N-oxides (84).[18,34,35] The cyclisations [(83a,b) ⟶ (84a,b)] are effected in high yield by heating with sodium methoxide in methanol. Under the same conditions (83c,d) fail to cyclise due to reduction of the basicity of



(83) (84)

	R^1	R^2
a;	H	H
b;	Br	Br
c;	H	NO_2
d;	NO_2	H

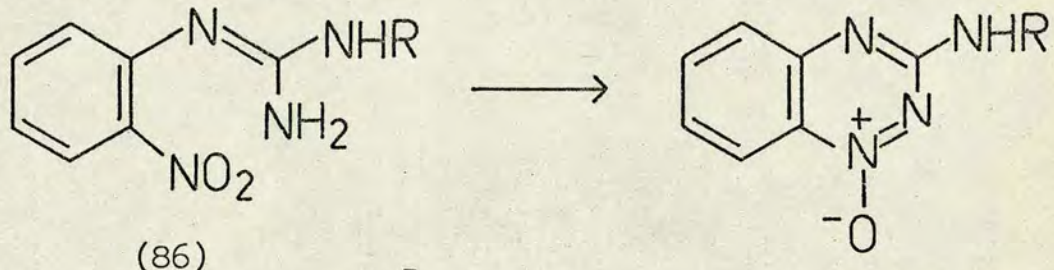


(85)

the amino group by the electron withdrawing nitro-group. However the deactivating effect of the nitro-group in (83d) can be overcome and cyclisation to the benzocinnoline (84d) result, when benzyltrimethylammonium hydroxide is used as the catalyst.[36] In the amino-nitrobiphenyl (85) the bulky bromo-substituents prevent the benzene rings assuming the coplanar arrangement necessary to permit interaction to occur and to allow the formation of a planar benzocinnoline product, so cyclisation fails[34] under a variety of basic conditions.

Formation of Benzo-1,2,4-triazine 1-N-Oxides

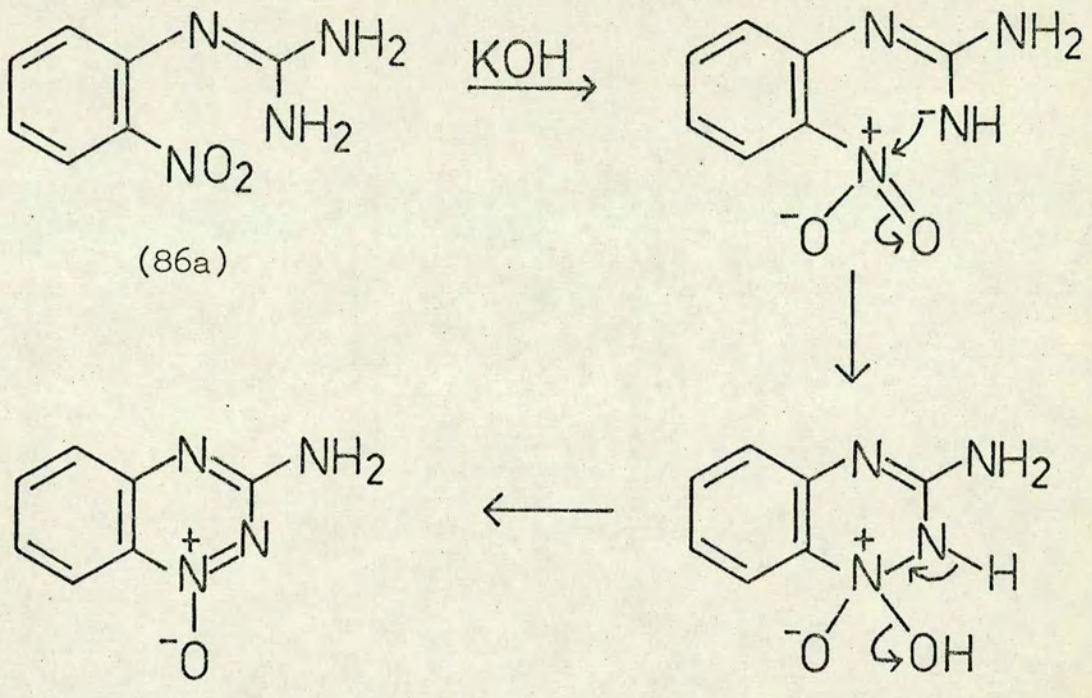
The base-catalysed ring closure of 2-nitrophenylguanidines (86) provides a valuable synthetic route to benzo-1,2,4-triazine 1-N-oxides (87).[37,38]



(86) (87)

R
a; H
b; Ph

These reactions would appear to be directly related to the cinnoline N-oxide synthesis already described but the fact that they are successful only under more severe conditions (heating under reflux with 40% w/v aqueous potassium hydroxide) may indicate mechanistic differences. One possibility is that the strong base may function by removing a proton from the amino-nitrogen inducing the aldol-type mechanism shown in (Scheme 17).

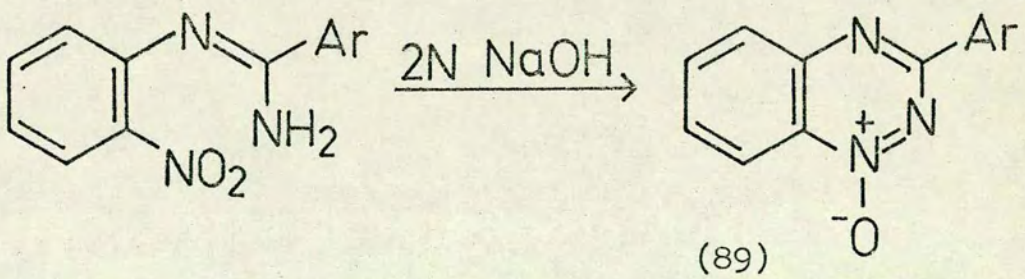


(86a)

(87a)

Scheme 17

The synthesis of 3-arylbenzo-1,2,4-triazine N-oxides (89) from 2-nitrophenylbenzamidines (88)[39] is clearly a similar reaction but requires a less severely basic medium.

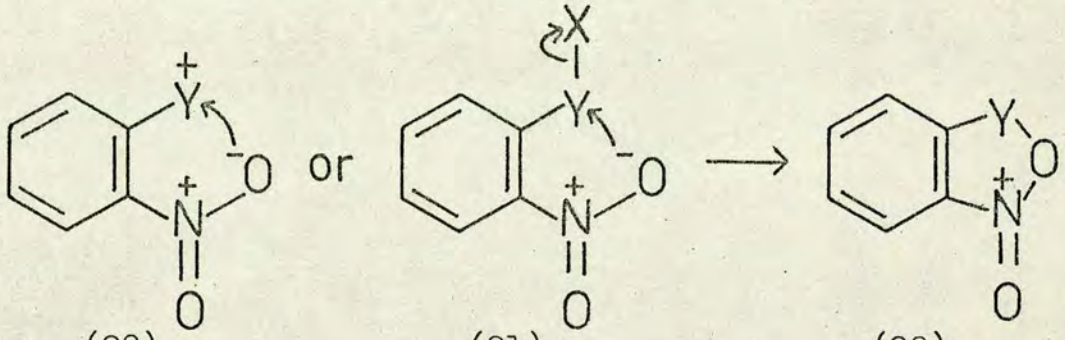


(88)

(89)

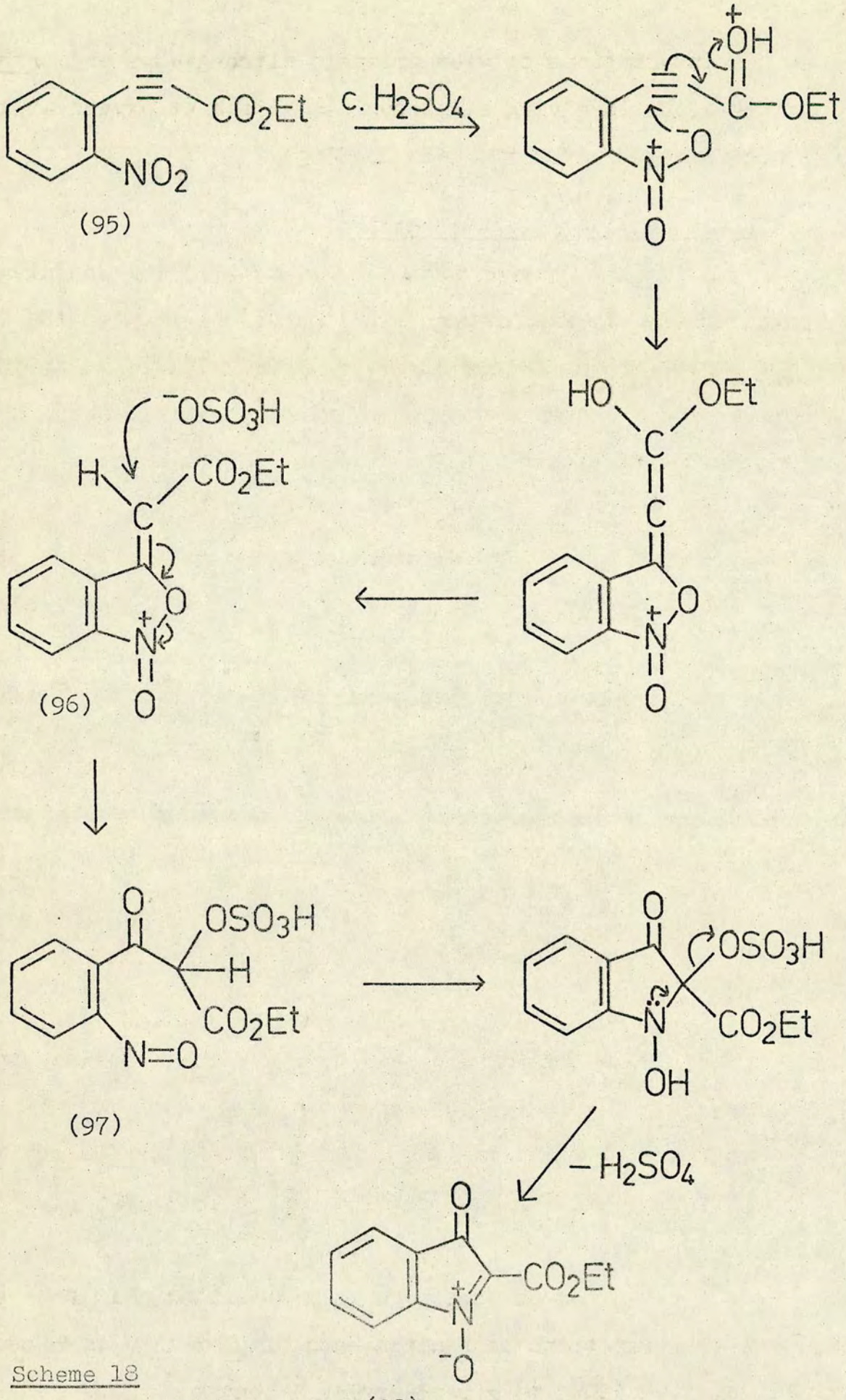
Reactions of ortho-Nitrobenzene Derivatives involving Intramolecular Electrophilic Attack at Oxygen

Clearly any intramolecular interaction [(90) or (91) → (92)] enlisting the nucleophilic character of an aromatic nitro-group will involve attack by the negatively charged oxygen atom of the nitro-group at an electron deficient (90) or potentially electron deficient (91) site in an ortho-side-chain.



(90) (91) (92)

In the previous section, reactions involving nucleophilic attack on the nitro-group were discussed. It is easy to select reactions belonging to that class since the carbon to nitrogen or nitrogen to nitrogen bond formed does not suffer further modification and so is present in the final product. Unfortunately such a clear-cut situation is not found in the electrophilic type of interaction. Thus it is common for the initial product [cf. (92)] formed by bonding between oxygen and the side-chain to undergo further electron reorganisation, thereby providing no evidence for its existence in the final product. In many cases, therefore, with experimental evidence lacking, the sole justification for postulating initial interaction of this type is that it often provides a mechanistic rationale for the process in question.



(95)

(96)

(97)

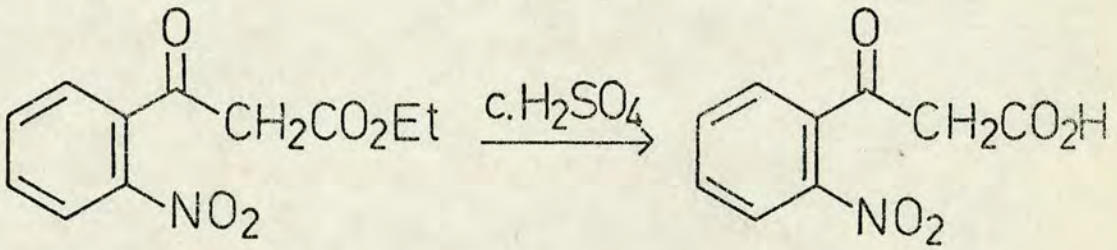
(98)

Scheme 18

Interactions between aromatic nitro-groups and ortho-side-chains involving electrophilic attack at oxygen will be considered under two main headings.

a) Electrophilic Attack at Carbon

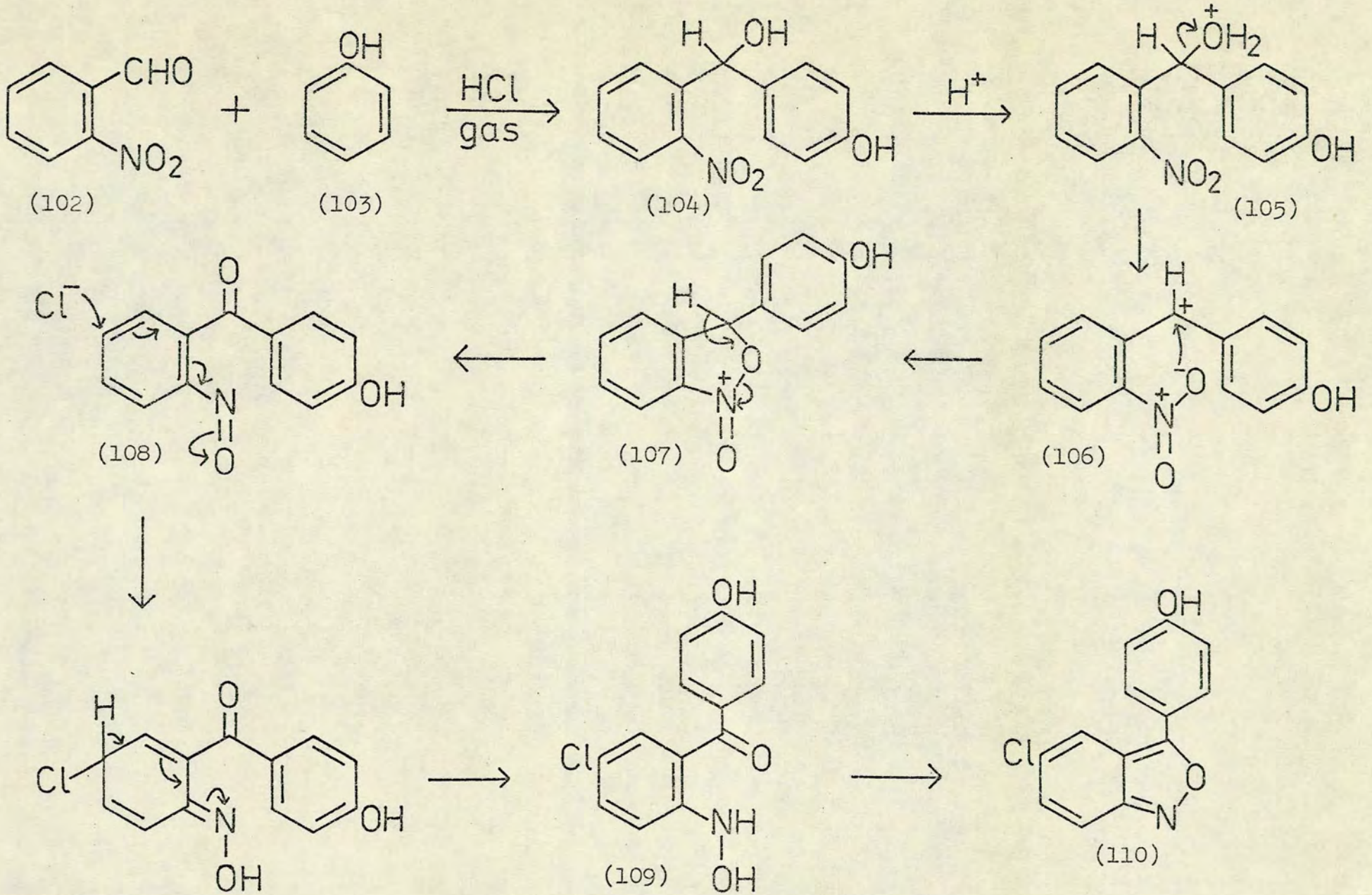
A feature of reactions of this type is that an oxygen atom is usually transferred from the nitro-group to the ortho-side-chain. This aspect is well illustrated by the conversion of ethyl 2-nitrophenylpropiolate (95) into 2-carbethoxyisatogen (98), catalysed by concentrated sulphuric acid.[40] It is unlikely that hydration of the acetylene is a significant step in the mechanism since ethyl 2-nitrobenzoylacetate (93), the product of hydration, is hydrolysed[41] to 2-nitrobenzoylacetic acid (94) when treated with concentrated sulphuric acid, no isatogenic ester being formed. A possible mechanism for isatogen formation



(93) (94)

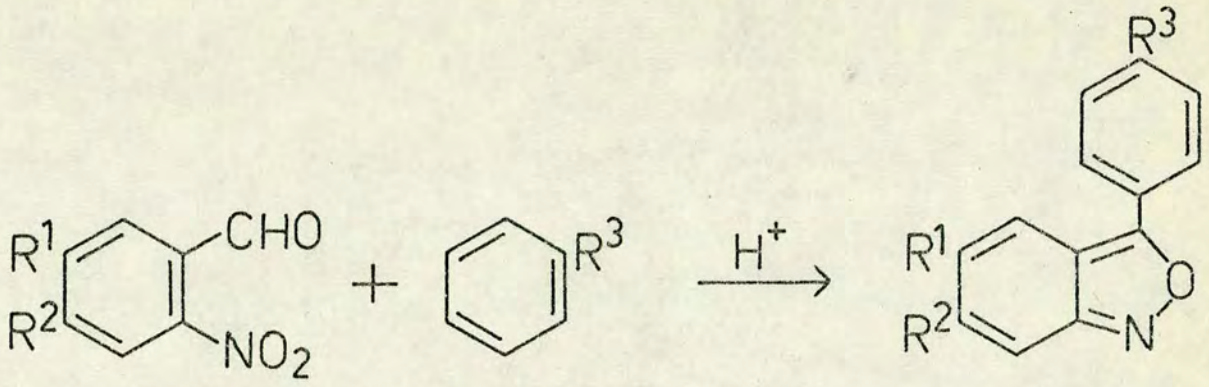
(Scheme 18) is initiated by direct interaction between the nitro-group and the ortho-side-chain in (95) forming the 5-membered intermediate (96). Ring-opening to the 2-nitroso-benzoyl compound (97) and subsequent cyclisation yields the isatogen (98).

Interaction of this type is also embodied in the acid-catalysed reactions of 2-nitrobenzaldehydes (99) with benzene derivatives (100) to give 3-aryl-2,1-benzisoxazoles



(102) (103) (104) (105) (106) (107) (108) (109) (110)

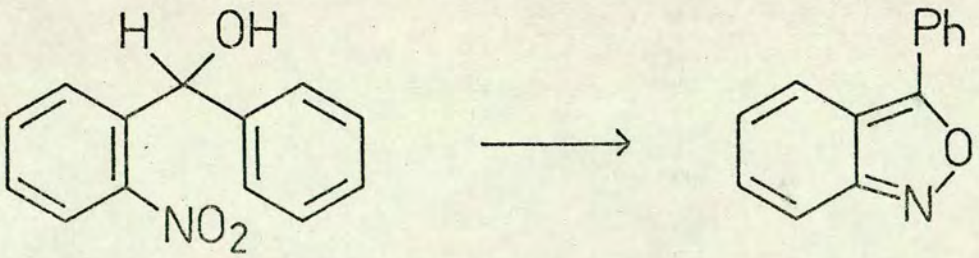
Scheme 19



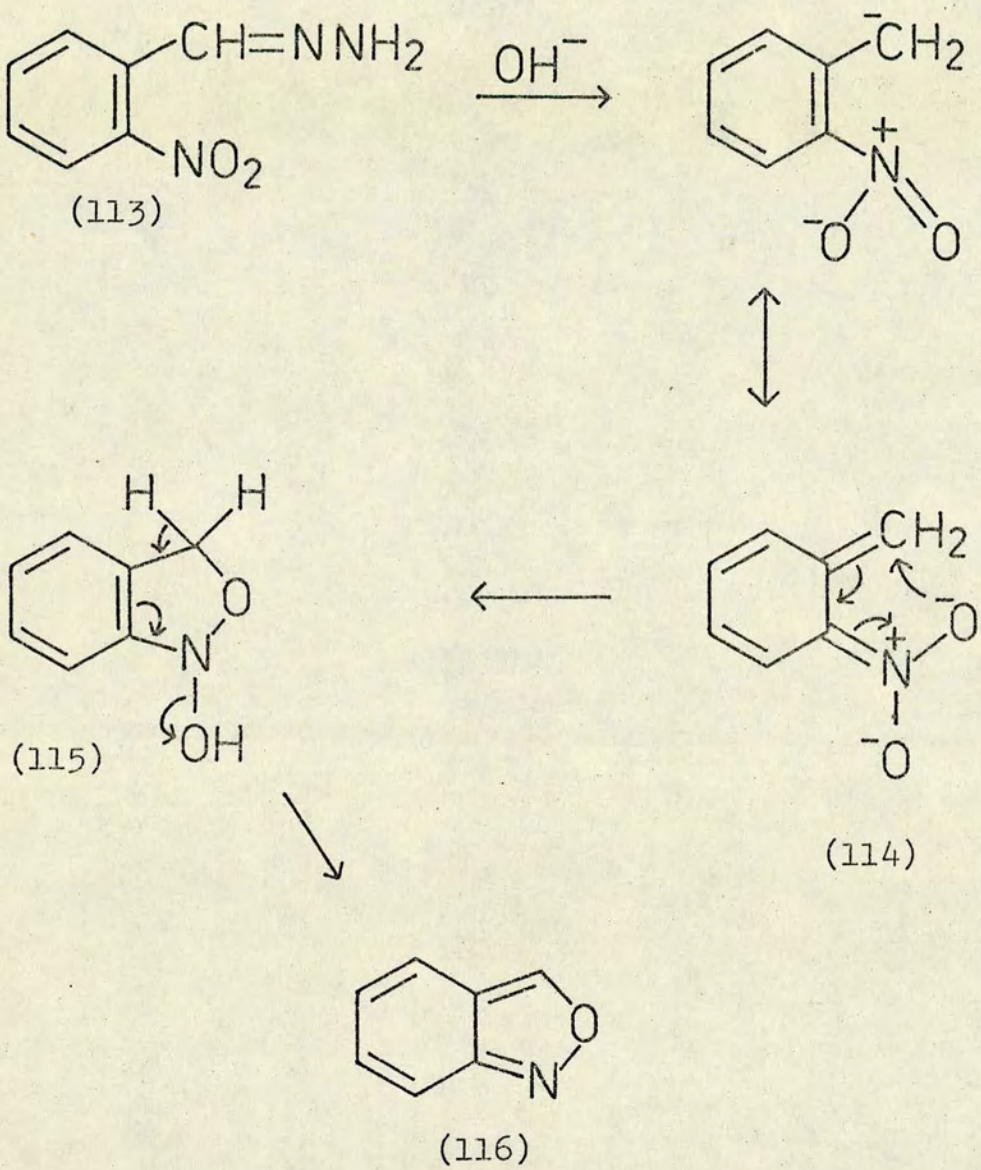
(99) (100) (101)

	R^1	R^2	R^3
a;	H	H	H
b;	H	H	OH
c;	H	NO_2	Br

(3-arylanthranils) (101).[42,43,44] Thus, 2-nitrobenzaldehyde (102) condenses with phenol (103) in the presence of hydrogen chloride to yield 5-chloro-3-(4-hydroxyphenyl)anthranil (110).[43] A plausible mechanism for this interesting transformation is given in Scheme 19. The intermediate formation of a benzhydrol derivative (104) in this type of reaction is supported by the observed conversion[45] under acidic conditions of 2-nitrobenzhydrol (111) into 3-phenylanthranil (112).



(111) (112)



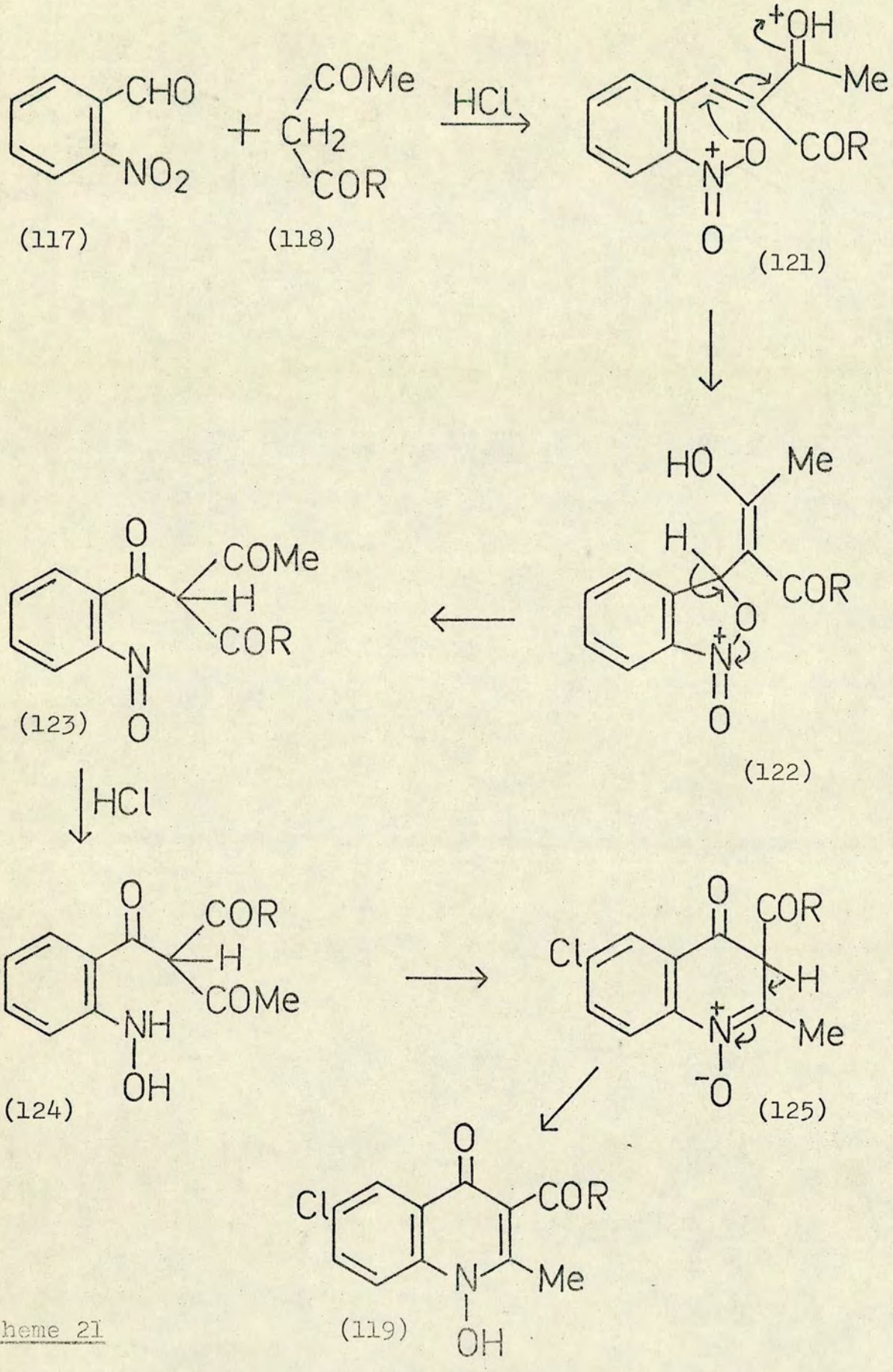
(116)

Scheme 20

The benzhydrol intermediate (104) then serves as a source of the benzhydryl cation (106) set up for interaction with the 2-nitro-group and subsequent oxygen transfer [(105) ⟶ (106) ⟶ (107) ⟶ (108)] to give the nitroso-benzophenone derivative (108). Subsequent conversion to the 4-chlorophenylhydroxylamine (109) finds analogy in the known transformation[46] by hydrogen chloride of nitrosobenzene into 4-chlorophenylhydroxylamine. The final step is a well documented[47] ortho-hydroxylaminoketone ⟶ anthranil transformation.

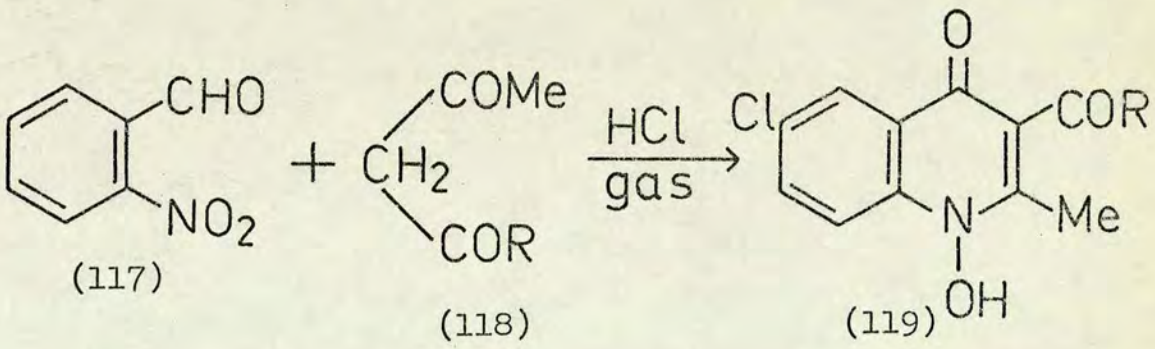
Though anthranil formation from ortho-nitrobenzene derivatives is normally acid-catalysed, some base-catalysed processes have been observed. Seibert[48] showed that treatment of 2-nitrobenzaldehyde hydrazone (113) with alkali gives a moderate yield of anthranil. This transformation can be explained (Scheme 20) by the initial formation of the resonance stabilised carbanion (114). Nucleophilic attack by oxygen on the side-chain in an intramolecular Michael-type addition yields the N-hydroxy heterocycle (115), dehydration of which affords the anthranil (116).

In reactions which are mechanistically related to the acid-catalysed anthranil syntheses already discussed, 2-nitrobenzaldehyde (117) condenses with active methylene compounds (118) containing at least one acetyl group to afford high yields of chlorinated N-hydroxyquinolinones (119).[43,49] The corresponding benzylidene derivatives (120) can also be isolated from such condensation reactions and their intermediacy in quinoline formation has been demonstrated.[43,49] Consequently the reactions leading to



(117) (118) (121) (122) (123) (124) (125) (119)

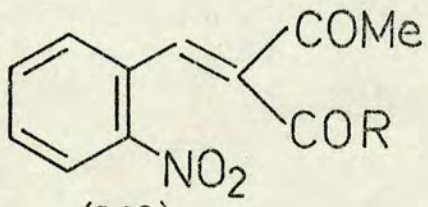
Scheme 21



(117) (118) (119)

[R = Me, Ph, OEt]

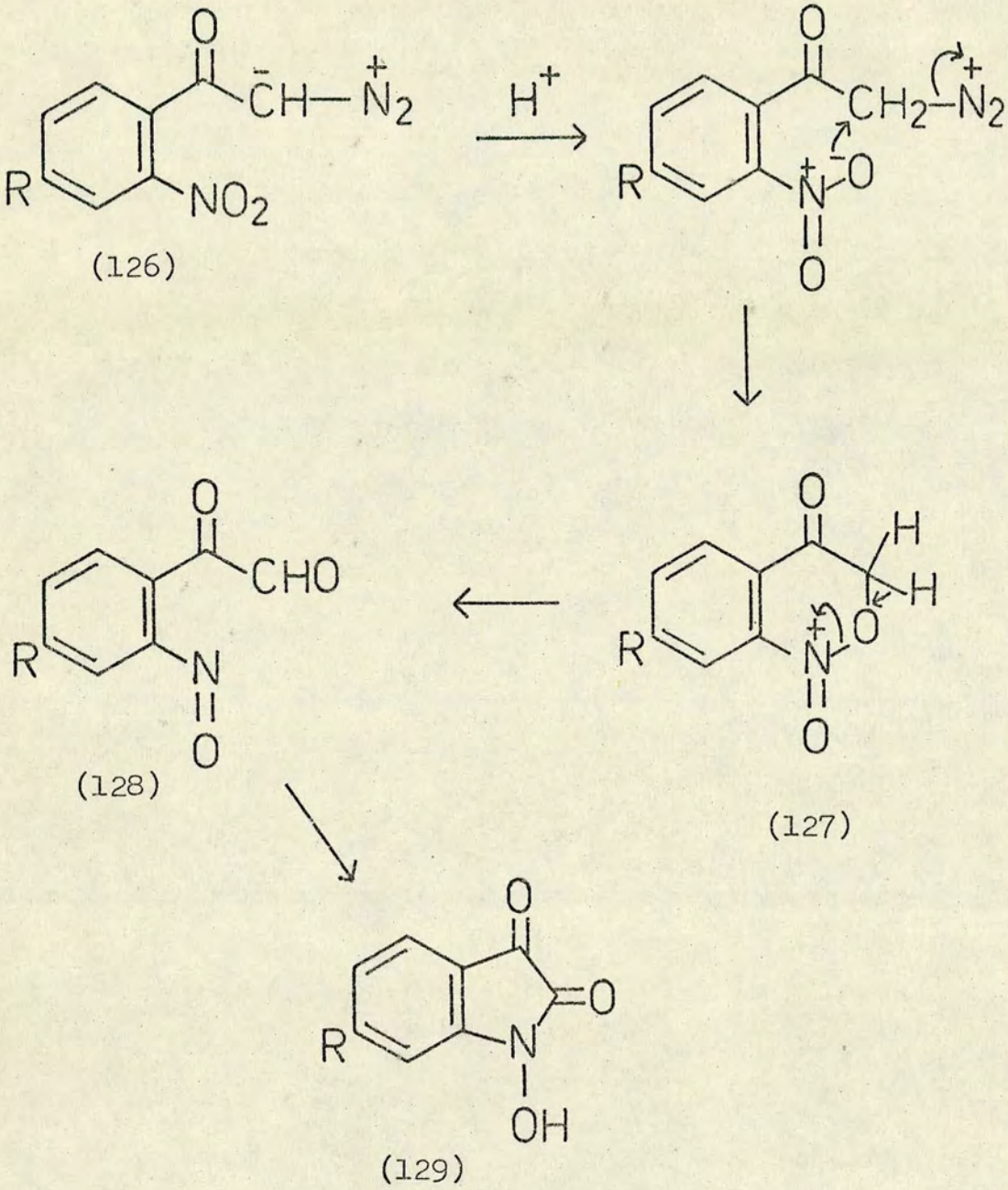
N-hydroxyquinolinones can be explained by a course (Scheme 21) which has a number of features in common with the mechanism



(120)

[R = COMe, CO_2Et]

proposed (cf. Scheme 19) for anthranil formation. Thus, electrophilic attack by the nitro-group on the protonated side-chain in the benzylidene derivative (121) would give the cyclic intermediate (122), subsequent ring-opening of which would give the nitroso-ketone (123). The subsequent steps [(123) → (124) → (125) → (119)] are then entirely analogous to those proposed in the anthranil syntheses (cf. Scheme 19). Despite the plausibility of this mechanism, a puzzling feature of the 2-nitrobenzaldehyde-active methylene condensation is the failure of apparently suitable 2-nitrobenzylidene derivatives (e.g. diethyl 2-nitrobenzylidenemalonate; ethyl 2-nitrobenzylidenecyanoacetate) to afford N-hydroxyquinolinones in the presence of hydrogen chloride.



(126)

(128)

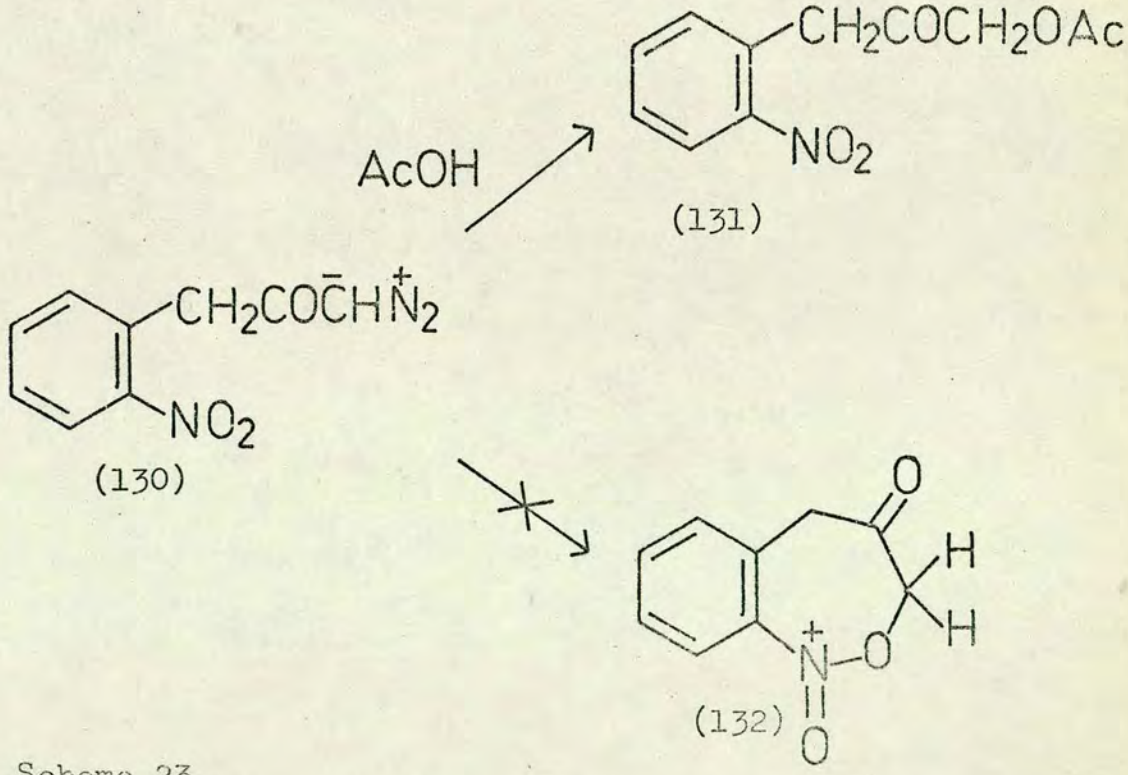
(127)

(129)

[R = H,MeO]

Scheme 22

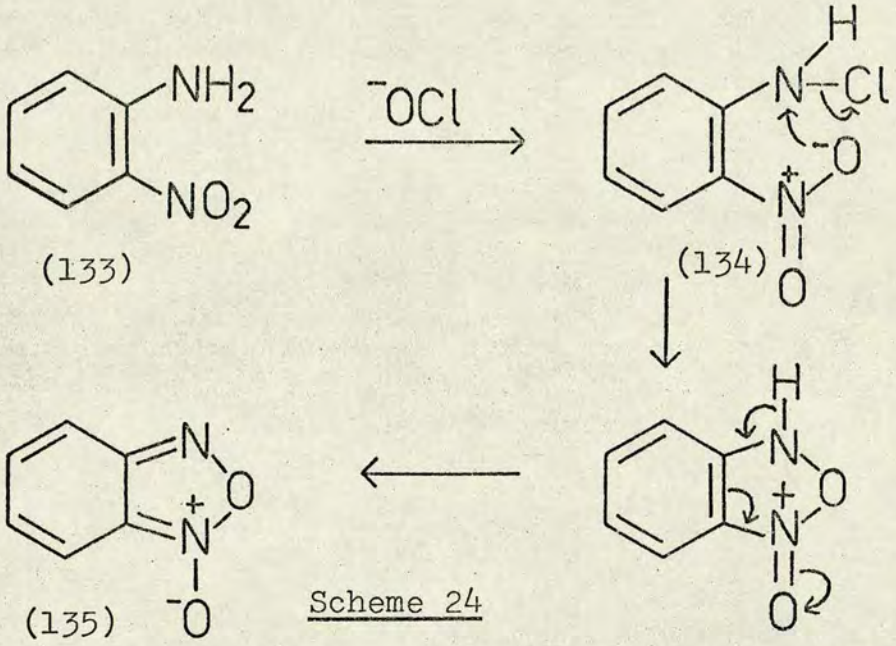
Relatively inaccessible 1-hydroxyisatins (129) are formed when substituted 2-nitrobenzoyldiazomethanes (126) are allowed to react under acidic conditions.[50,51] Reactions of this type can be explained[52] by a course involving electrophilic attack on the side-chain [(126) → (127); Scheme 22] oxygen transfer [(127) → (128)] to give the nitroso-intermediate (128) and subsequent cyclisation [(128) → (129)]. This mechanism is supported[52] by the fact that the homologous diazoketone (130) reacts normally with acids [(130) → (131); Scheme 23] without participation by the nitro-group. It is noteworthy that interaction between the ortho-nitro-group and the side chain in (130) would require the formation of a less stable seven-membered intermediate (132) thereby precluding involvement of the nitro-group.



Scheme 23

b) Electrophilic Attack at Nitrogen

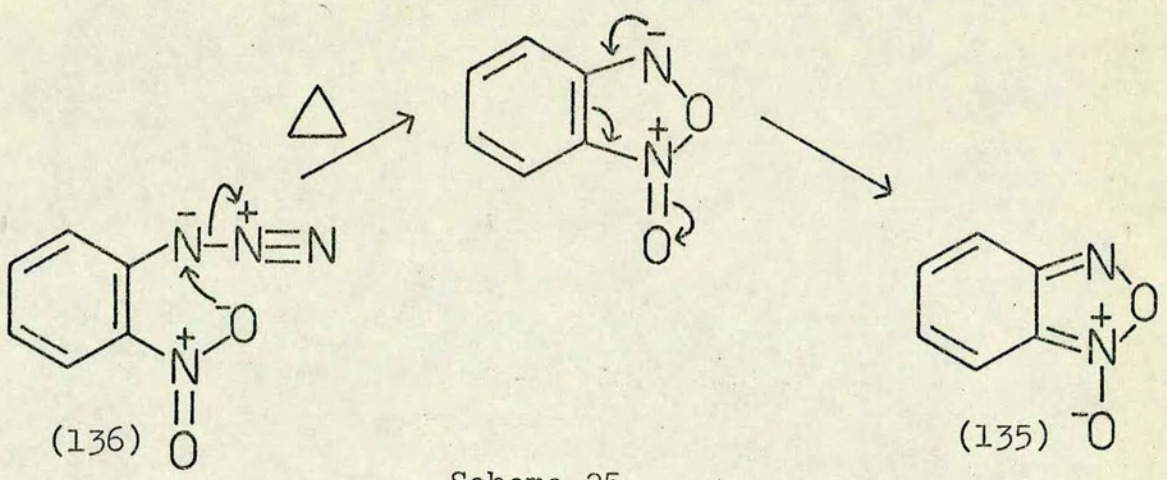
Reactions involving interaction between an aromatic nitro-group and an electron deficient nitrogen centre in an ortho-side-chain are rare. Probably the most common examples are cyclisations leading to benzofuroxans (135). Thus, hypochlorite oxidation[53,54] of ortho-nitroanilines (133) can be formulated[55,56] (Scheme 24) as occurring by initial electrophilic attack by the nitro-group on an N-chloro-amino side-chain in an intermediate of the type (134).



(135)

Scheme 24

The closely related formation of benzofuroxans (135) by thermolysis of 2-nitrophenylazides (136)[57] can be explained by a similar mechanism[58] (Scheme 25) in which the leaving group in the side-chain is nitrogen rather than chloride ion. In accord with participation by the nitro-group as outlined in Scheme 25, thermolysis of 2-nitrophenylazides (136) occurs at significantly lower temperatures than in the case of phenylazides.



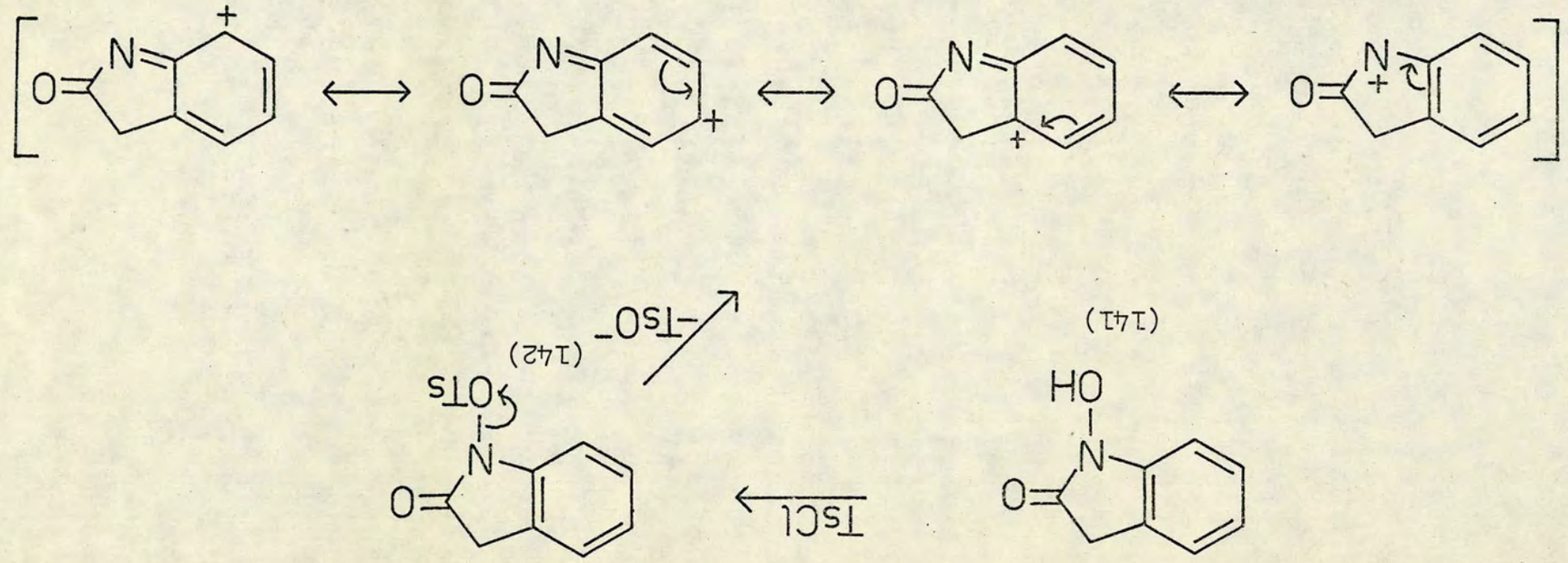
(136) (135)

Scheme 25

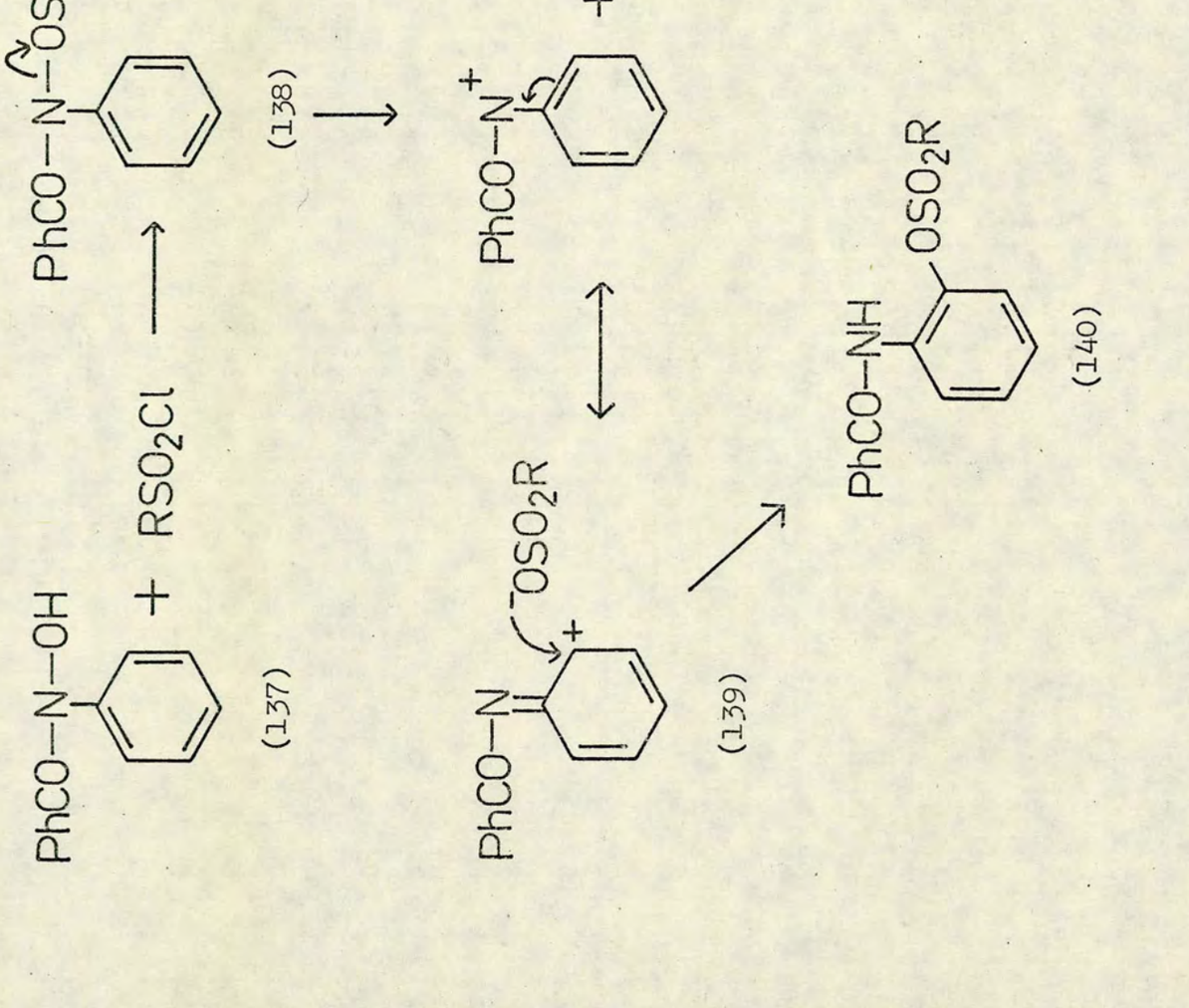
The subject material of the present thesis is concerned with studies of the base-catalysed reactions of some ortho-nitrobenzoyl derivatives and the synthesis and acid-catalysed reactions of substituted ortho-nitrophenylethylene oxides.

Chapter Two

Some Studies of Base-Catalysed Cyclisation Reactions of ortho-Nitrobenzoyl Derivatives



Scheme 27

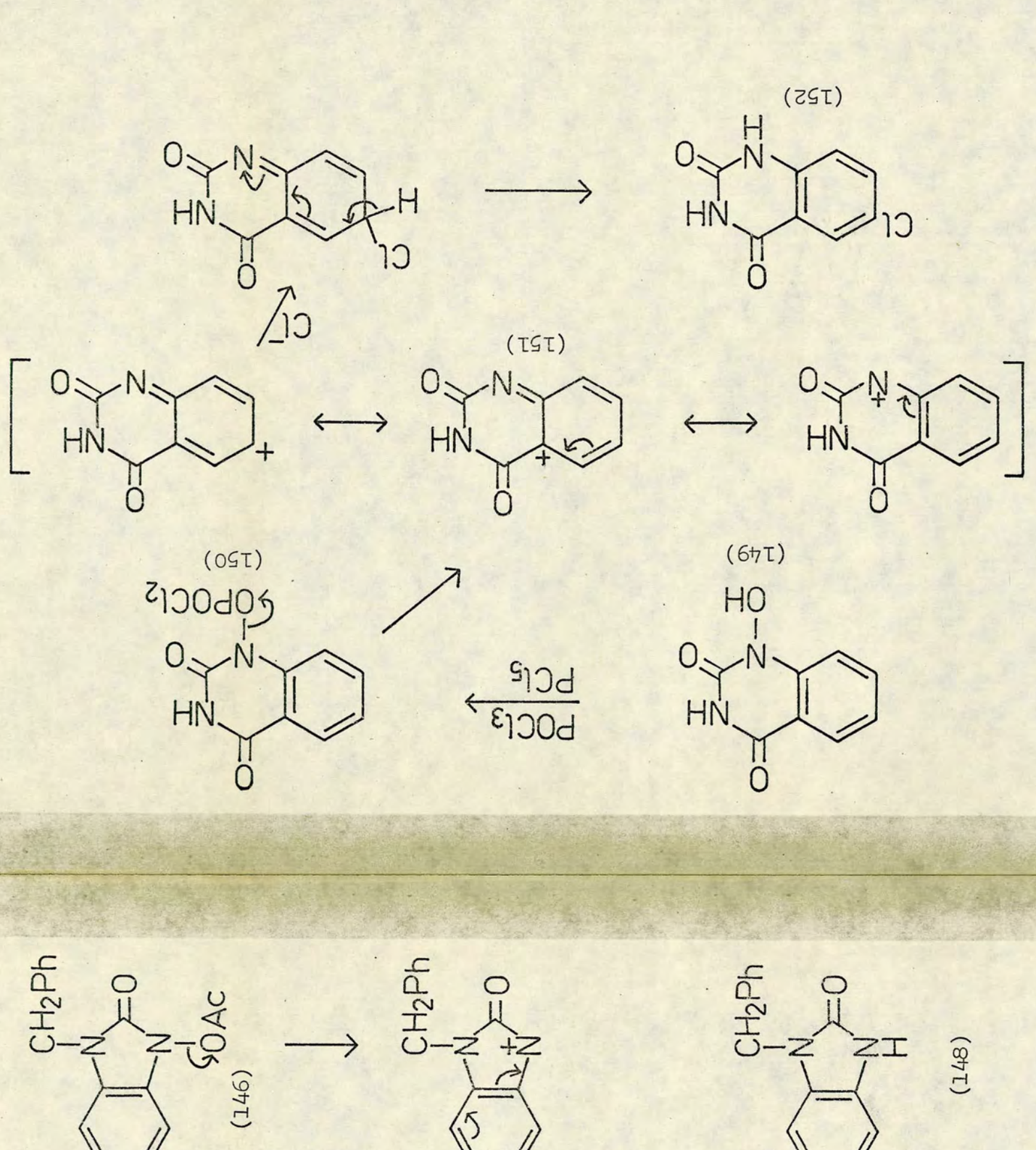


Scheme 26

2.1 Extensions of an N-Hydroxyquinazoline Synthesis

The intermediate formation of nitrenium ions in a variety of solvolytic and rearrangement processes is still controversial.[59] Such nitrogen cations are believed[59,60] to be produced by the heterolytic cleavage of the nitrogen-chlorine bond in N-chloroamines. More recently N-hydroxyamino-derivatives[61] have attracted attention as potential nitrenium ion precursors. Thus the reaction[62] of N-benzoylphenyl-hydroxylamine (137) with toluene-p-sulphonyl chloride catalysed by triethylamine affords almost exclusively the ortho-toluenesulphonate (140). This result is rationalised (Scheme 26) by tosylation at the hydroxylamino function with subsequent ionisation [(137) ⟶ (138) ⟶ (139)] to the resonance stabilised nitrenium ion (139). Recapture of the toluenesulphonyloxy anion at the ortho-position [(139) ⟶ (140)] then accounts for the formation of the rearrangement product (140).

N-hydroxy heterocycles are of particular interest as potential sources of heterocyclic nitrenium ions. Treatment[63] of 1-hydroxyoxindole (141) with toluene-p-sulphonyl chloride at low temperature produces the unstable tosylate (142) which is converted by warming with methanol into a mixture of the 5-methoxyindole (143) and the 7-methoxyindole (144). These transformations can be interpreted in terms of nitrenium cation intermediates (Scheme 27). Conversion of the N-hydroxyl function by tosylation into a good leaving group [(141)⟶(142)] and scission of the nitrogen-oxygen bond in the ester (142) can lead to a resonance stabilised



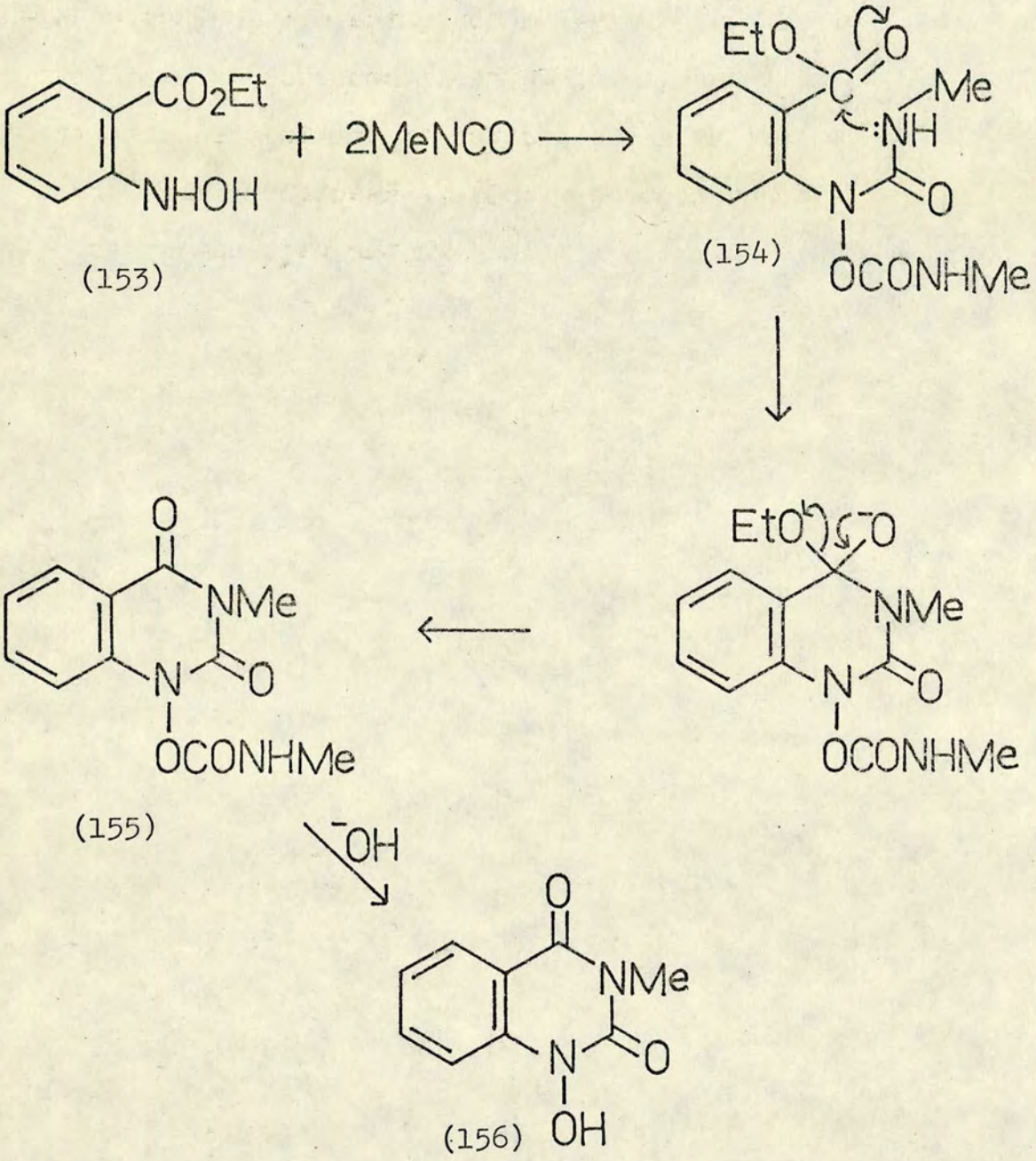
Scheme 28

Scheme 29

nitrenium ion whose reaction with methanol at the 5- and 7-positions in the benzene nucleus rationalises the products formed. The reaction of 3-benzyl-1-hydroxybenzimidazole (145) with acetic anhydride under reflux affords 5-acetoxy-3-benzylbenzimidazole (148).[64] A plausible mechanism (Scheme 28) involves nucleophilic attack on the initially formed N-acetoxy intermediate (146) either in a concerted manner or subsequent to ionisation to the resonance stabilised nitrenium cation (147).

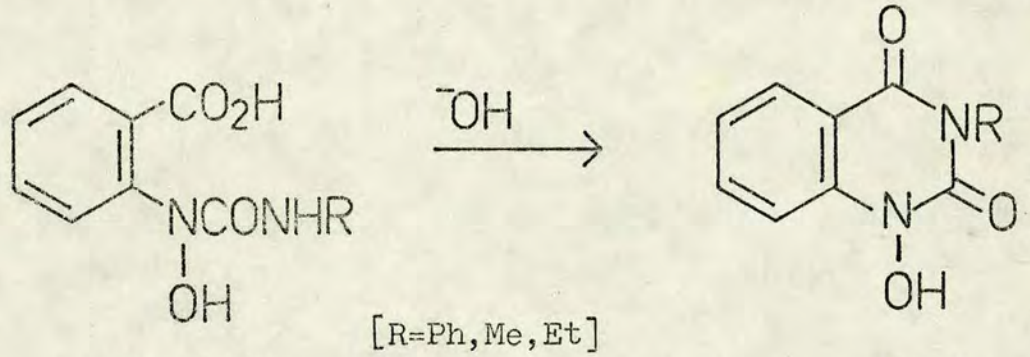
A related process may be operating in the formation[65] of 6-chloroquinazoline-2(1H),4(3H)-dione (152) by heating 1-hydroxyquinazoline-2(1H),4(3H)-dione (149) under reflux with a mixture of phosphorus oxychloride and phosphorus pentachloride. The first step (Scheme 29) is the formation of the dichlorophosphate ester (150) which suffers nucleophilic substitution by chlorine either directly or after ionisation to the resonance stabilised nitrenium ion (151). However the detailed study of this type of reactivity in 1-hydroxyquinazolinones is hampered by the relative inaccessibility of such heterocycles in general. Consequently flexible synthetic routes to N-hydroxyquinazolinones are of interest.

A number of syntheses of 1-hydroxyquinazolinones based on phenylhydroxylamine derivatives have been described but are of limited generality due to the relative inaccessibility of suitable starting materials. Thus the reaction[66] of ethyl 2-hydroxyaminobenzoate (153) with methyl isocyanate in the presence of ethanolic potassium hydroxide as catalyst


CO2Et
NHOH
+ 2MeNCO
EtO
O
Me
:NH
N
O
OCONHMe
(153)
(154)
NMe
OCONHMe
(155)
-OH
(156)
OH

Scheme 30

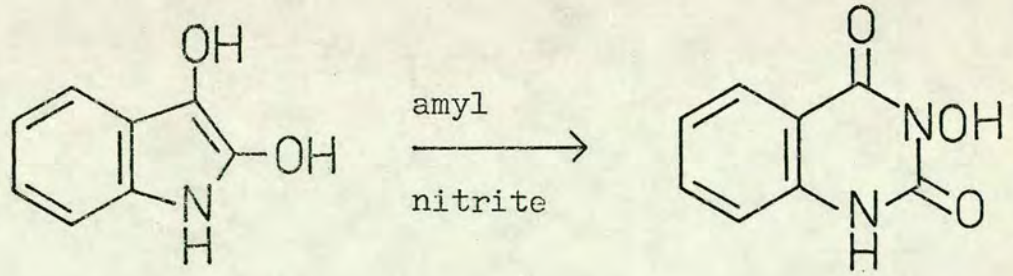
affords the 1-hydroxyquinazolinone (156). The initially formed di-amide (154) (Scheme 30) cyclises by nucleophilic attack of nitrogen on the ester function to yield the quinazolinedione derivative (155), alkaline hydrolysis of which yields 1-hydroxy-3-methylquinazoline-2(1H),4(3H)-dione (156). Although this synthesis proceeds in excellent yield it is of limited scope because of the inaccessibility of the hydroxylamino precursor (153). Reactions which are presumably mechanistically similar are the base-catalysed cyclisations[67] of the amides (157) to the 3-substituted



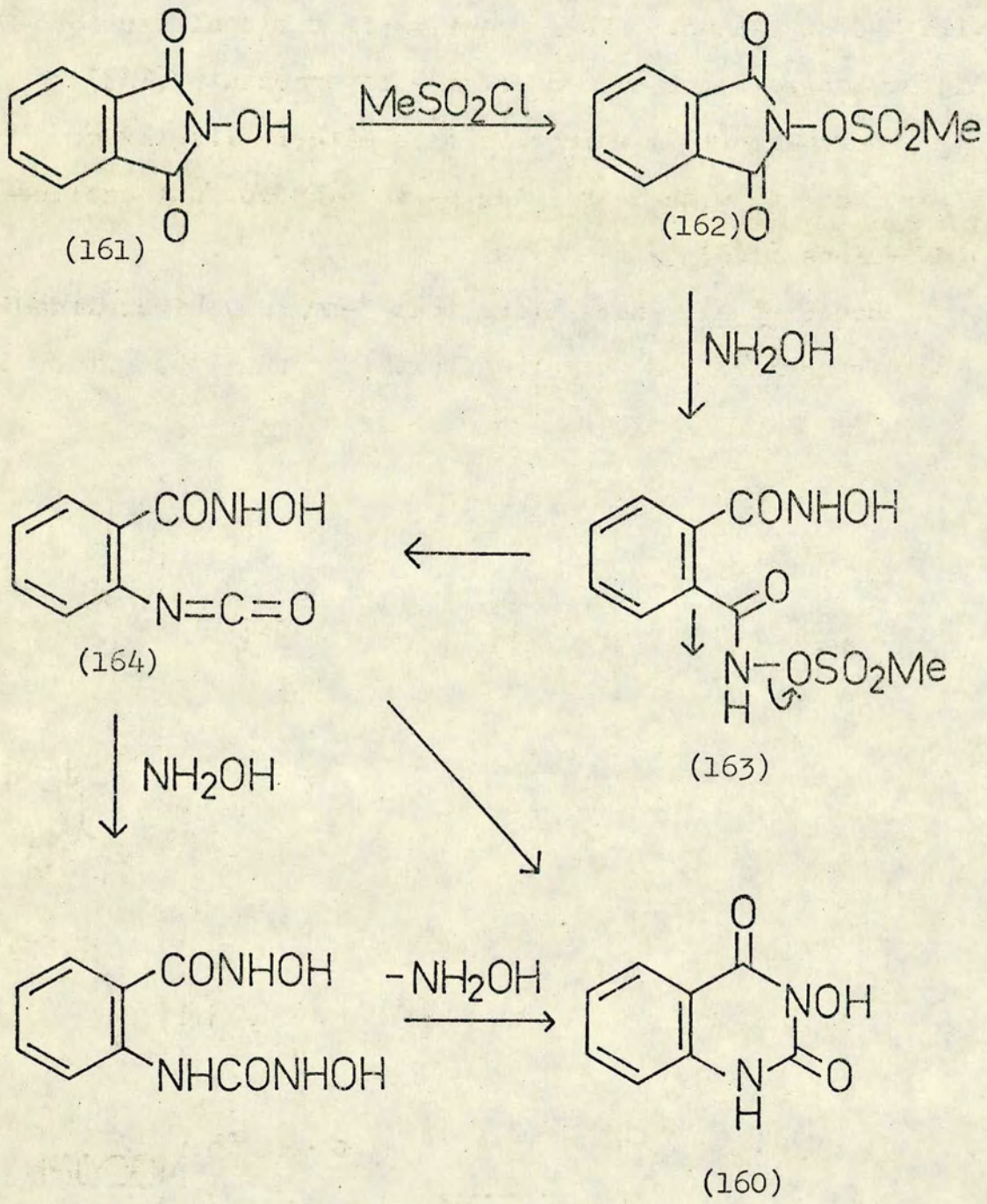
(157) (158)

1-hydroxyquinazolinediones (158).

No derivatives of 3-hydroxyquinazolinediones have been prepared but the parent compound (160) has been synthesised[68]



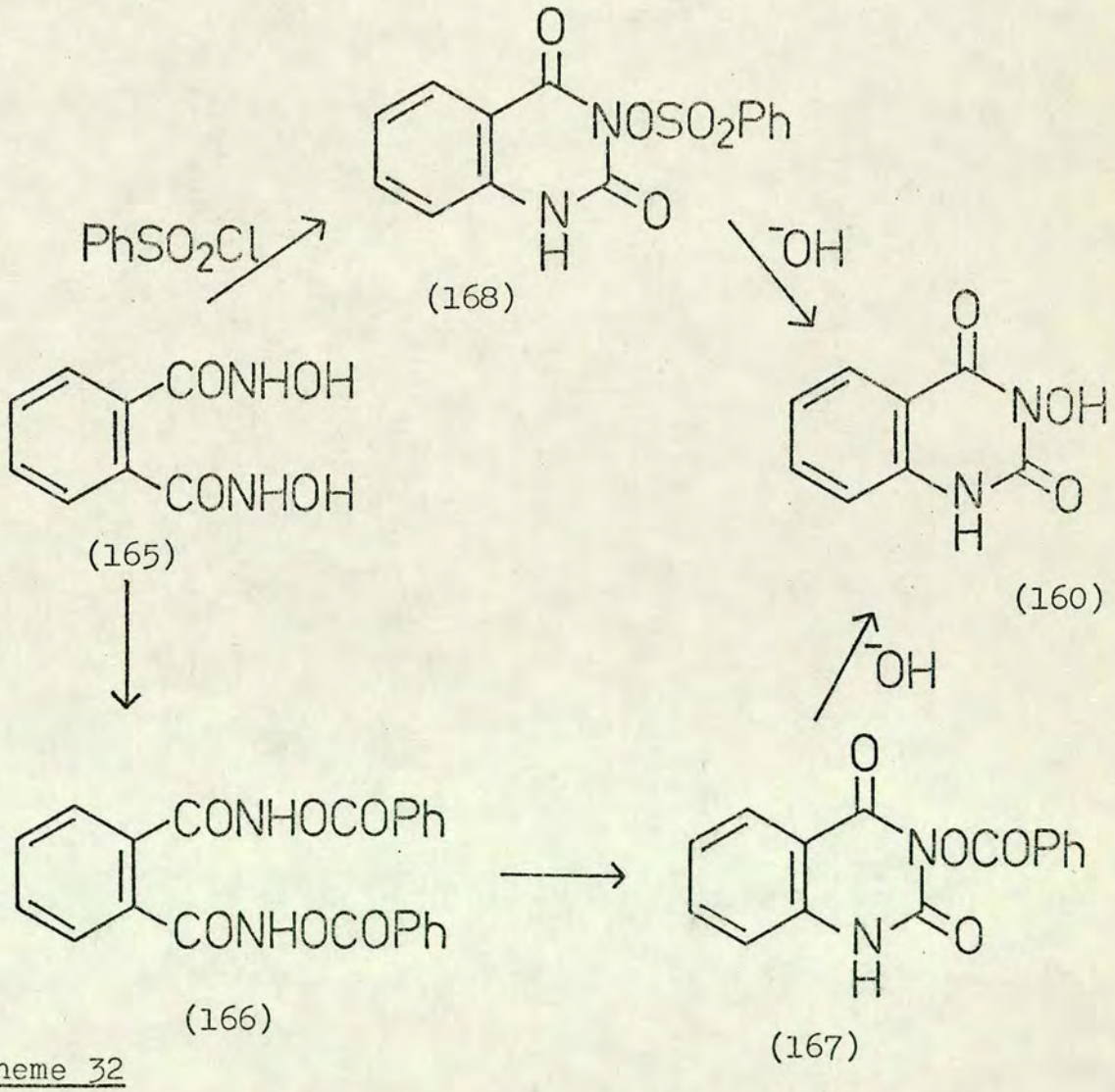
(159) (160)


O
N-OH
O
(161)
MeSO2Cl
O
N-OSO2Me
O
(162)
NH2OH
CONHOH
O
N-OSO2Me
H
(163)
CONHOH
N=C=O
(164)
NH2OH
CONHOH
NHCONHOH
-NH2OH
O
NOH
N
H
O
(160)

Scheme 31

by the action of amyl nitrite on 2,3-dihydroxyindole (159). The compound (160) is also produced by the reaction[69] of the methanesulphonyl derivative (162) of N-hydroxyphthalimide (161) with hydroxylamine. This reaction is rationalised (Scheme 31) by Lossen rearrangement of the intermediate (163) to the isocyanate (164) which cyclises either directly or after reaction with hydroxylamine to 3-hydroxyquinazoline-2(1H), 4(3H)-dione (160).

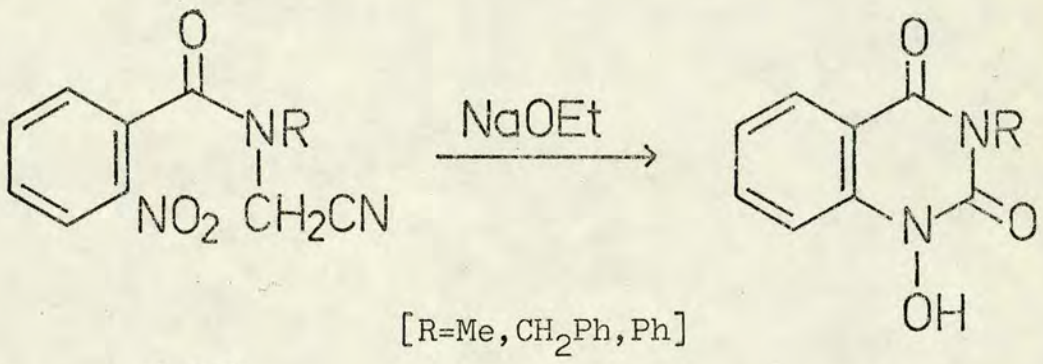
Bauer et al. have shown that 3-hydroxyquinazolinedione (160) is formed from phthalohydroxamic acid (165) either by



Scheme 32

reaction with benzenesulphonyl chloride[70] or via the dibenzoyloxy derivative (166)[71] (Scheme 32). Both reactions must involve a Lossen-type rearrangement as invoked in the previous mechanism (Scheme 31). The final step in both transformations is hydrolysis of the 3-benzenesulphonyloxy (168) and 3-benzoyloxy (167) derivatives respectively.

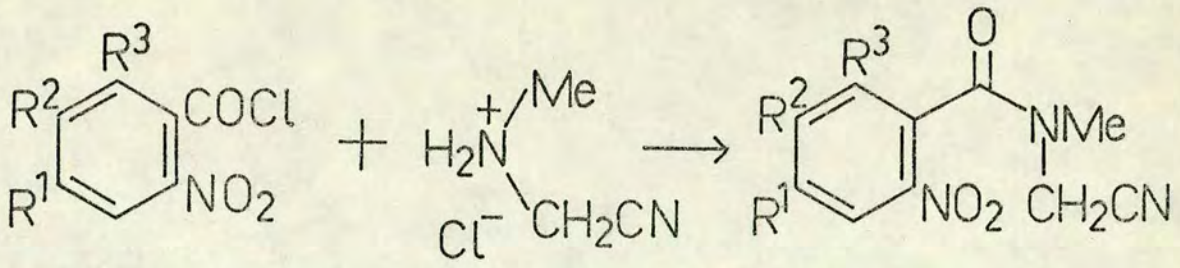
Work carried out in this department[72] had shown that the base-catalysed cyclisation of readily accessible N-substituted N-cyanomethyl 2-nitrobenzamides (169) affords high yields of 1-hydroxyquinazoline-2(1H),4(3H)-diones (170).



(169) (170)

In view of the relative inaccessibility of 1-hydroxyquinazolinones (see before) it was decided to study the scope and utility of this type of synthesis.

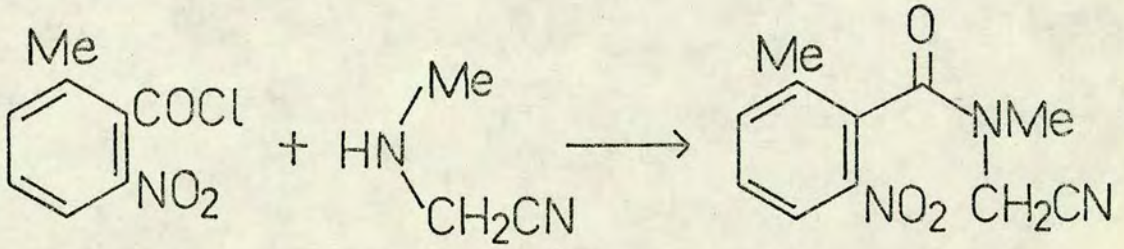
The main advantage of the synthetic method [(169)→(170)] is that the starting amides (169) are readily available. The parent 2-nitrobenzoic acids are either commercially available or accessible by nitration of the corresponding benzoic acids. The amides (172a,b,d and e) were thus synthesised in excellent yield (>80%) by condensation of the corresponding 2-nitrobenzoyl chlorides (171a,b,d and e) with N-methylamino-



(171) (172)

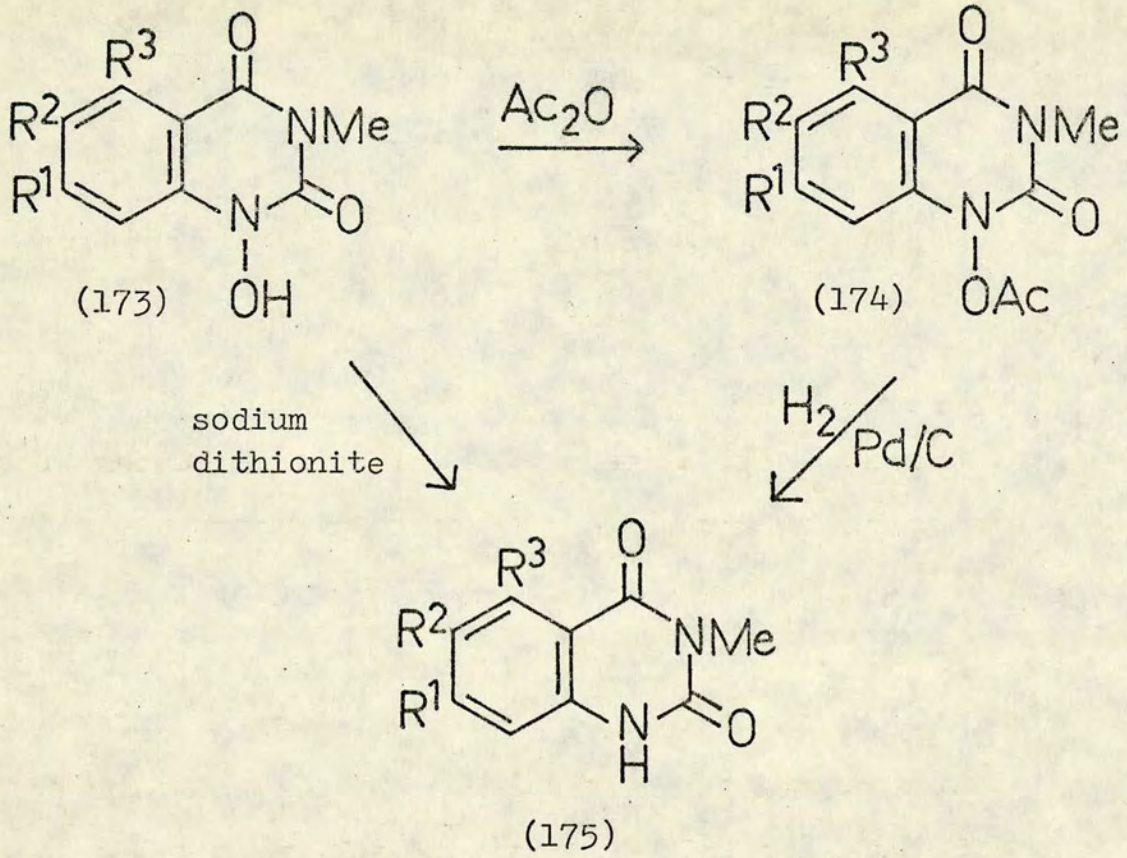
	R^1	R^2	R^3
a;	H	Cl	H
b;	H	Me	H
d;	Cl	H	H
e;	H	H	NO_2

acetonitrile hydrochloride in the presence of sodium acetate in glacial acetic acid. This method was unsuccessful in the

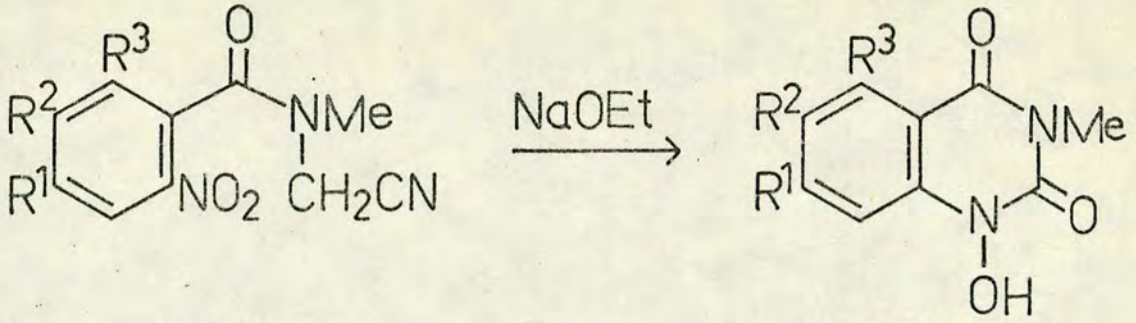


(171c) (172c)

preparation of the amide (172c). This compound was obtained by condensing the acid chloride (171c) with a two-fold excess of the free N-methylaminoacetonitrile in benzene, the amine then functioning as the condensation catalyst. When the amides (172a-d) were heated under reflux with sodium ethoxide in ethanol they were converted in high yield (>80%) into substituted 1-hydroxy-3-methylquinazoline-2(1H),4(3H)-



	R^1	R^2	R^3
a;	H	Cl	H
b;	H	Me	H
c;	H	H	Me
d;	Cl	H	H
e;	H	H	H

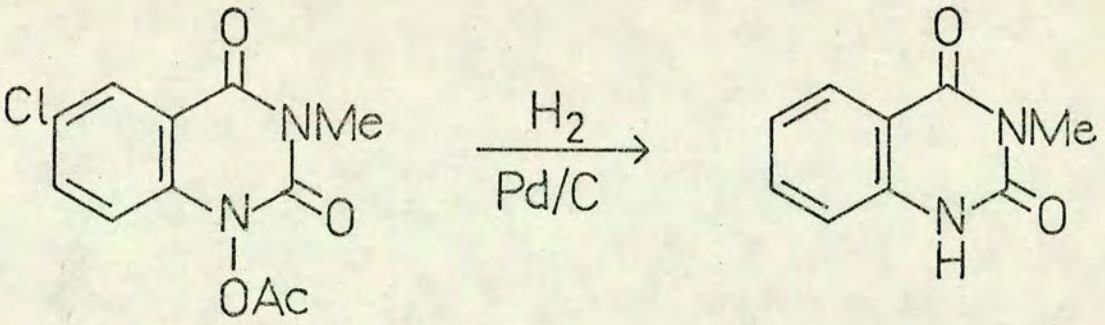


(172) (173)

	R^1	R^2	R^3
a;	H	Cl	H
b;	H	Me	H
c;	H	H	Me
d;	Cl	H	H

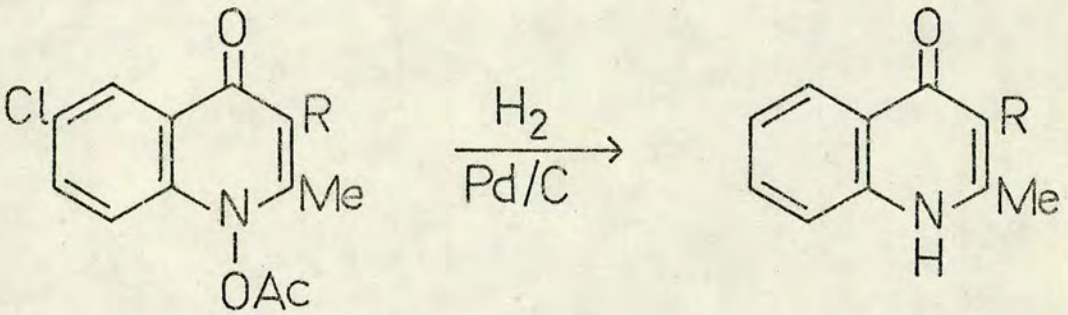
diones (173a-d). Similar treatment of the dinitroamide (172e) produced only an intractable brown solid. Attempts to effect the cyclisation of the amide (172e) under milder conditions using aqueous sodium carbonate, aqueous sodium acetate or piperidine as the catalysts yielded only unreacted starting amide. The 1-hydroxyquinazolinediones (173a-d) were identified by their i.r. spectra which showed no absorption due to a nitro-group but contained bands at ca 3100, 1700 and 1650 cm^{-1} attributable to the 1-hydroxyquinazoline-2(1H),4(3H)-dione nucleus. Confirmation of the presence of the N-hydroxy group was provided by the ready formation of N-acetoxy derivatives (174a-d) having characteristic[4] carbonyl absorption at 1800 cm^{-1} in their i.r. spectra. Reduction of the 1-hydroxyquinazolinediones (173a-d) with sodium dithionite afforded the quinazoline-2(1H),4(3H)-diones (175a-d). These compounds were identical to the products obtained by catalytic hydrogenolysis of the N-acetoxy derivatives (174a-d) with the exception that (174a) yielded

the known[72] 3-methyquinazoline-2(1H),4(3H)-dione (175e).



(174a) (175e)

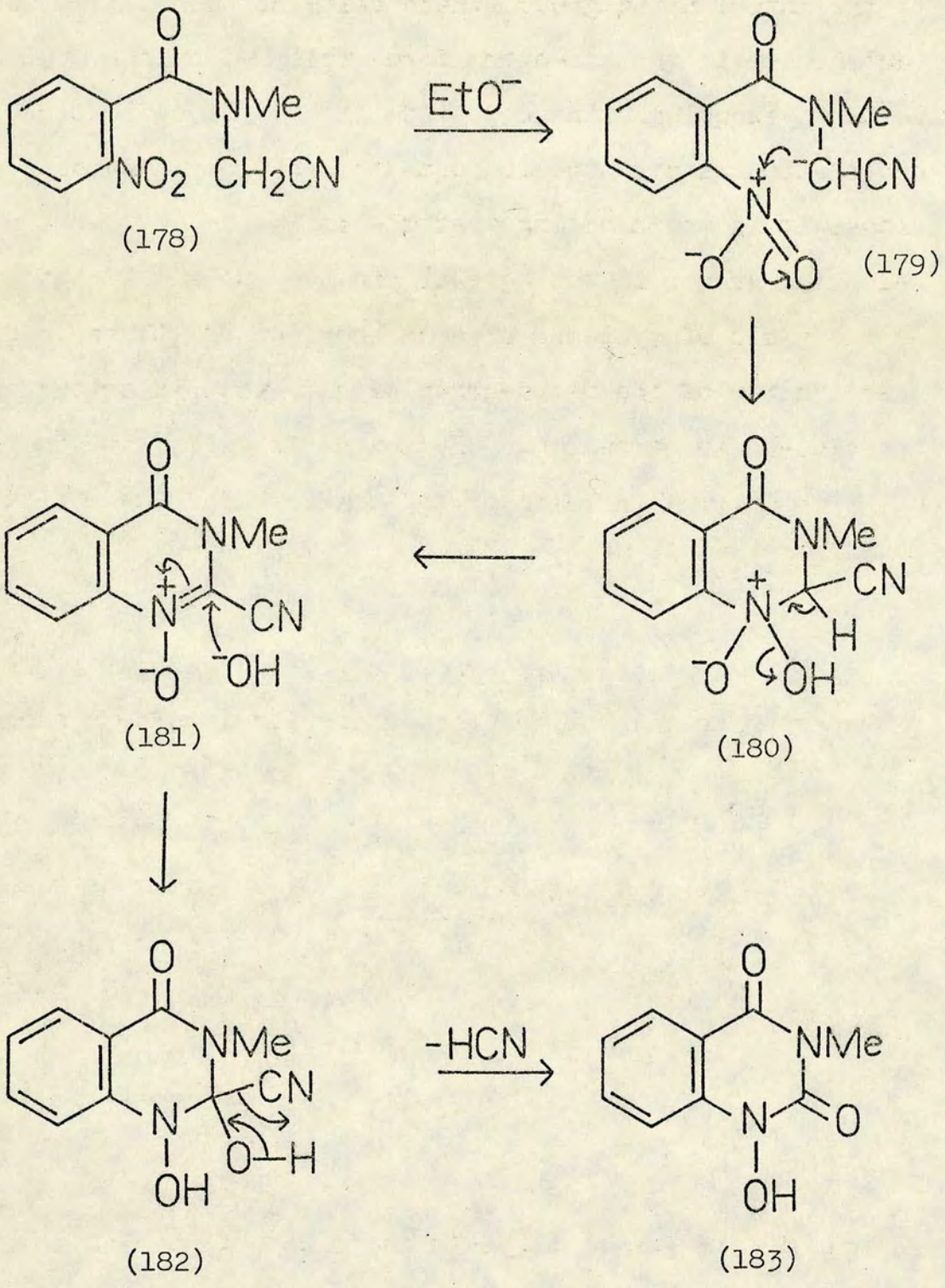
Loss of chlorine has been observed[49] previously in the hydrogenolysis of 1-acetoxy-6-chloroquinolines (176) when



(176) [R=H, CO_2Et] (177)

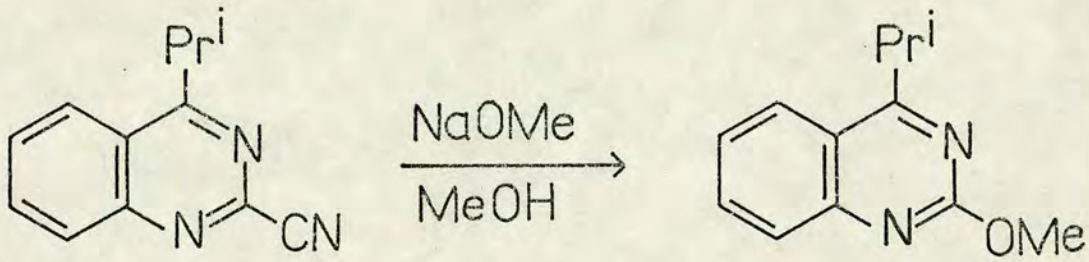
the acetoxy group and the chlorine atom were both replaced by hydrogen producing the quinolines (177). It is interesting to note that the chlorine atom in (174d) was not substituted by hydrogen and it may be significant that it was only the chlorine atom para to the N-acetoxy function which was replaced.

A plausible mechanism for the cyclisation of the amides (172a-d) to the 1-hydroxyquinazolinediones (173a-d) is shown in Scheme 33. The initial steps [(178)⟶(179)⟶(180)⟶(181)]



Scheme 33

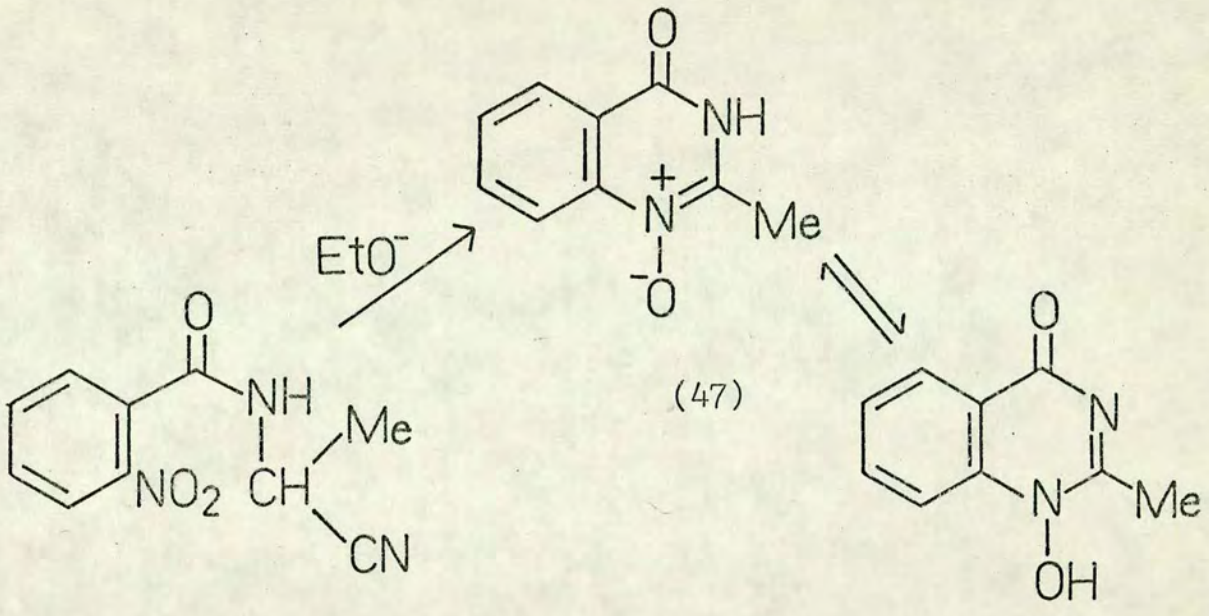
involve the aldol-type addition of the side-chain carbanion to the intact nitro-group (there being no possibility of tautomerism to the aci-nitro form) followed by dehydration to the cyanoquinazolinone N-oxide (181). In evaluating this cyclisation as a synthetic route to 1-hydroxyquinazolinediones it is worth noting that the inclusion of electron-releasing groups in the benzene ring has no adverse effect on the yield of cyclised product showing that there is no deactivation of the nitro-group with respect to attack by the side-chain carbanion. Hydroxide ion attack at the 2-position in (181) results in the formation of the hydrate (182) which, by loss of hydrogen cyanide, yields the 1-hydroxyquinazolinedione (183). The latter stages of this mechanism [(181)→(182)→(183)] are supported by the ease with which the cyano-group in the 2-cyanoquinazoline (184) suffers nucleo-



(184) (185)

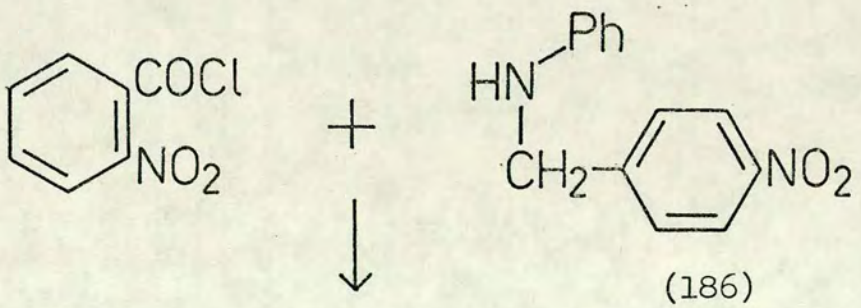
philic displacement[73] to yield the 2-methoxyquinazoline (185).

The evidence for an N-oxide intermediate (181; Scheme 33) in cyclisations of the type [(178)→(183)] is based solely on the base-catalysed conversion of the amide (46) (see page 11) into the quinazolinone N-oxide (47). The tautomeric

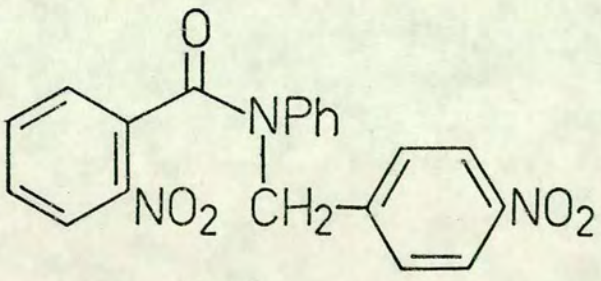


(46)

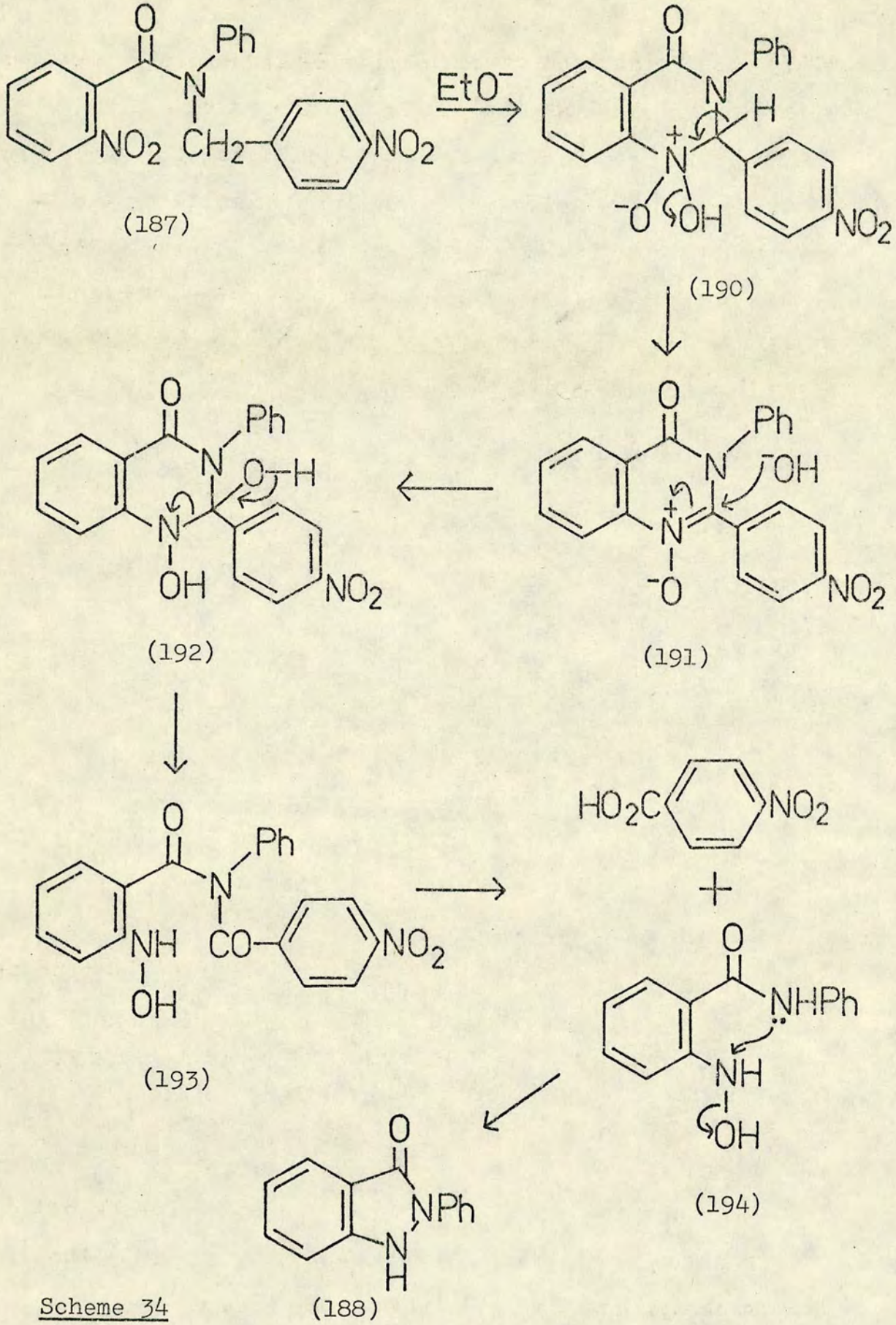
nature of (47) with the resultant higher electron density at the 2-position must provide the necessary deactivation to inhibit subsequent nucleophilic attack by hydroxide ion (Scheme 33). However it was desirable to obtain further evidence that an N-oxide was involved in the cyclisations of the amides of the type (178). With this aim the amide



(186)

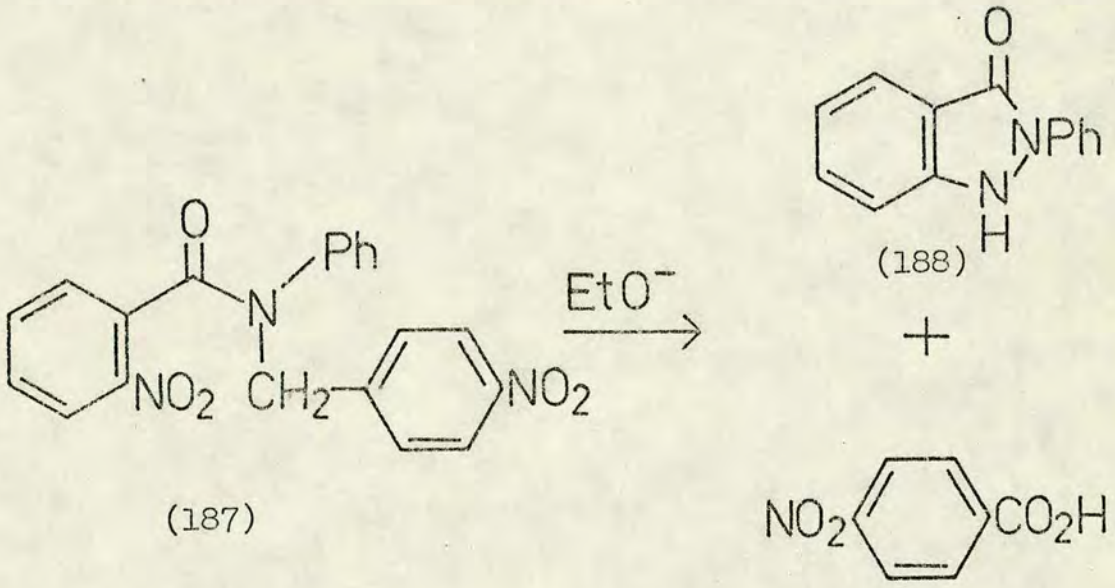


(187)


Ph
N
O
NO2
CH2
NO2
EtO⁻
H
OH
(187)
(190)
(191)
(192)
(193)
(194)
(188)
HO2C
NO2
NHPh
NH
CO

Scheme 34

(187) was synthesised by condensing 2-nitrobenzoyl chloride with 4-nitrobenzylaniline (186).[74] The amide (187) was chosen in the hope that as well as providing the necessary activation of the methylene group for cyclisation, the 4-nitrophenyl substituent would exert a stabilising influence on any N-oxide intermediate. In practice the ethoxide-catalysed cyclisation of the amide (187) did not afford an N-oxide product but instead N-phenylindazolone (188) and

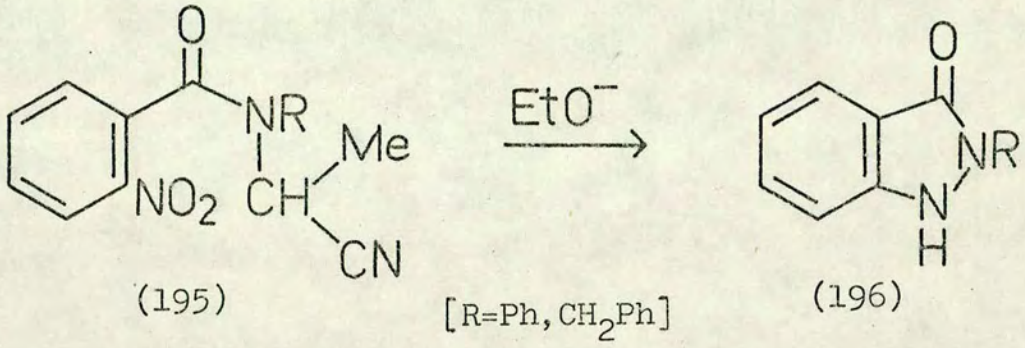


(187) (188) (189)

4-nitrobenzoic acid (189) were produced. The formation of these products can be rationalised by a course (Scheme 34) initiated by base-catalysed cyclodehydration [(187)→(190)→(191)] to the quinazolinone N-oxide intermediate (191) which undergoes attack by base affording the hydrate (192). However this hydrate (192), in contrast to (182; Scheme 33) can only achieve stabilisation by ring-opening to (193), the 4-nitrophenyl substituent being a poor leaving group. Hydrolysis of the amide (193) produces 4-nitrobenzoic acid

and cyclisation of the anilide (194) yields N-phenylindazolone (188).

Indazolone (196) formation is also observed[72] in the cyclisation of the N,N-disubstituted 2-nitrobenzamides (195) and a mechanism analogous to Scheme 34 has been proposed.



(195) [R=Ph, CH_2Ph] (196)

2.2 Studies of Intramolecular Nucleophilic Aromatic Substitution Reactions Leading to Phthalimidines

Nucleophilic Aromatic Substitution Reactions

Nucleophilic substitution at an aromatic carbon atom resembles the analogous process in aliphatic compounds in that a charged or neutral nucleophile replaces an atom or group on a ring position in an aromatic molecule, the displaced group leaving with its bonding electrons. The structure of aromatic molecules - a σ-bonded structure between two π-electron orbitals - favours electrophilic substitution reactions involving attack by an electron-deficient species. However suitably substituted aromatic compounds can undergo ready nucleophilic substitution. Three main mechanisms of aromatic nucleophilic substitution are recognised.

(a) The Unimolecular Mechanism

This is the aromatic equivalent of the aliphatic S_N1 mechanism and involves rate-determining ionisation of the aromatic substrate to yield an aromatic cation (Ar^+)

$$Ar - X \longrightarrow Ar^+ + X^- \xrightarrow{Y^-} Ar - Y$$

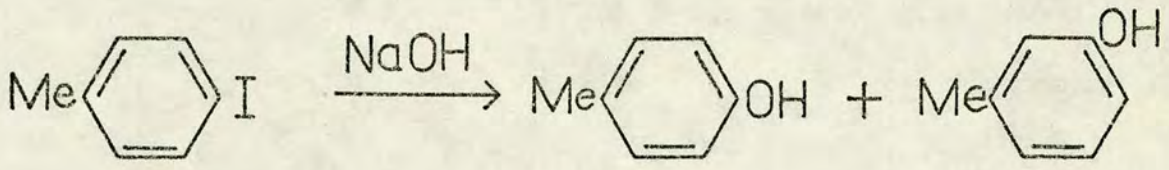
which rapidly combines with a nucleophile (Y^-). There are reasons why an aromatic S_N1 mechanism is less probable than its aliphatic counterpart. Since the vacant orbital in the aromatic cation is at right angles to the delocalised π-electron orbitals the positive charge cannot be stabilised by conjugation but only by the inductive effect which is much less efficient in the aromatic system. Also, a decrease in steric strain is often a driving force in the formation of an aliphatic cation in S_N1 reactions but this is unlikely

in the case of an aromatic substrate.

There are a few reactions for which the unimolecular mechanism appears to be favoured. Of these the most thoroughly investigated[75,76,77] is the decomposition of aryldiazonium ions in aqueous media which has been shown to follow first order kinetics.

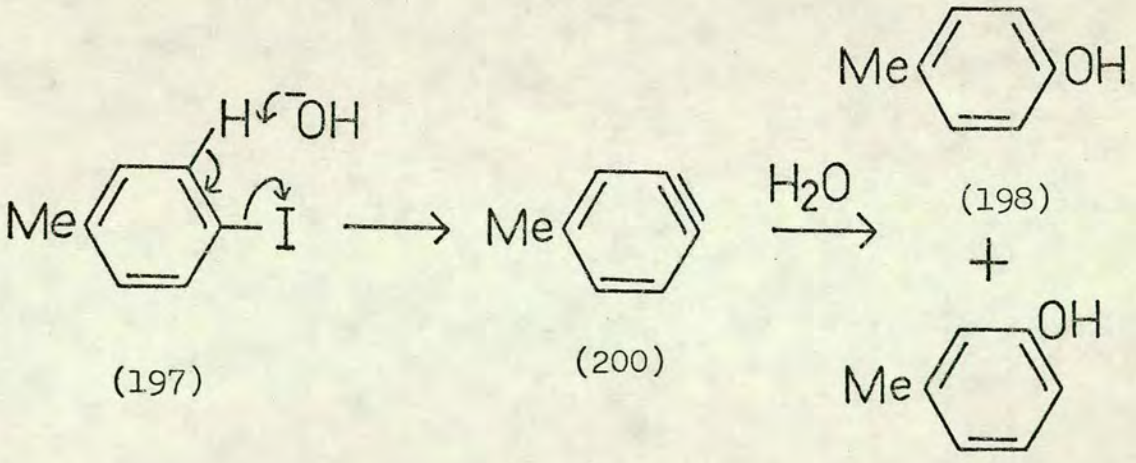
(b) The Elimination-Addition (Benzyne) Mechanism

Some nucleophilic substitution reactions performed under strongly basic conditions result in cine-substitution (substitution with rearrangement). The reaction[78] of para-



(197) (198) (199)

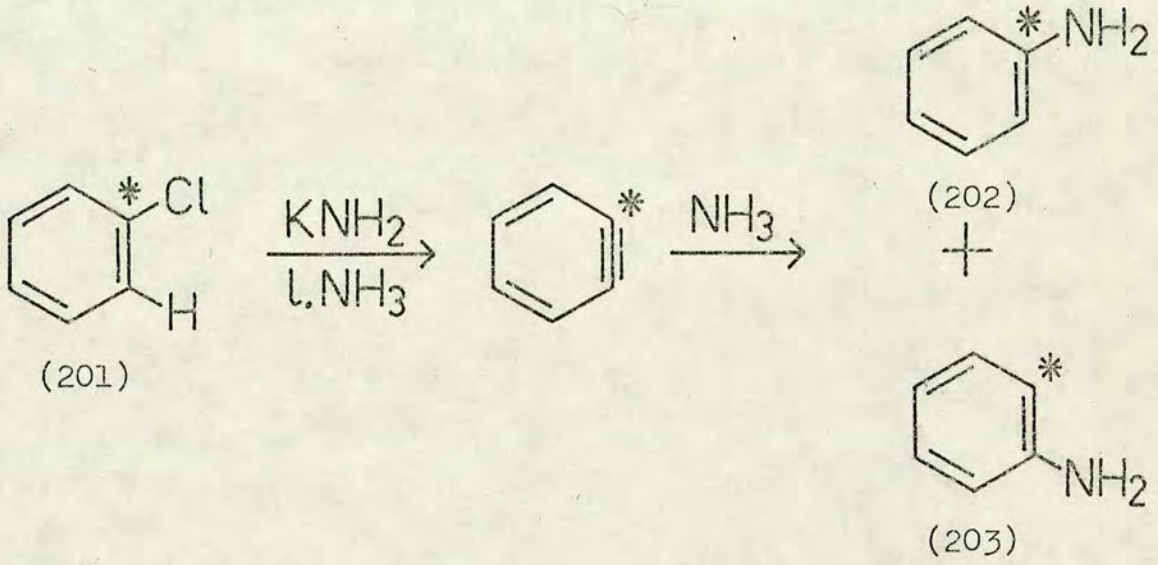
iodotoluene (197) with aqueous sodium hydroxide at 340° affords para-cresol (198)(51%) and meta-cresol (199)(49%). These transformations are accommodated by a mechanism



(197) (200) (199)

Scheme 35

(Scheme 35) involving the elimination of hydrogen iodide, initiated by proton abstraction by the strong base, to yield the di-dehydrobenzene (benzyne) intermediate (200). Addition of water to (200) accounts for the formation of the isomeric cresols (198) and (199). The operation of this mechanism has also been demonstrated[79,80] in the reaction of chlorobenzene-1-^{14}C (201) in liquid ammonia to produce aniline-1-^{14}C (202)

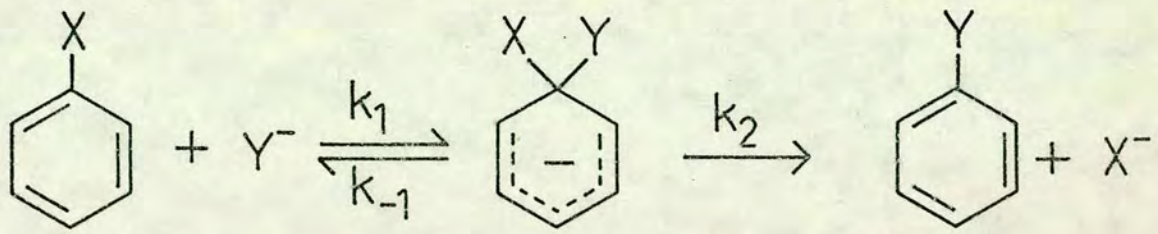


(201) (202) + (203)

and aniline-2-^{14}C (203) in almost equal amounts.

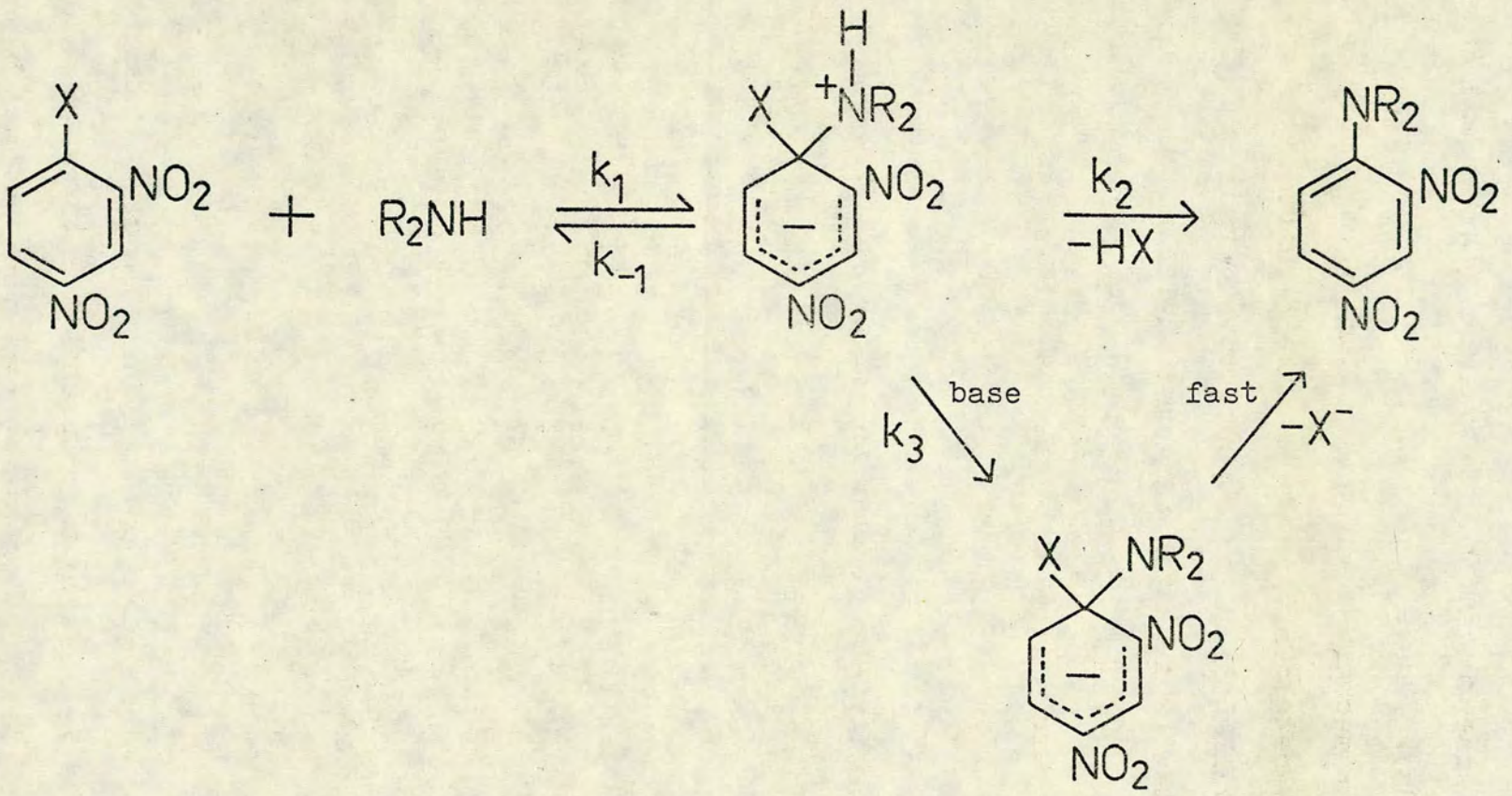
(c) The Addition-Elimination Mechanism

The majority of aromatic nucleophilic substitution reactions follow a multi-step addition--elimination mechanism (Scheme 36). The evidence supporting this type of mechanism is considerable.



(204)

Scheme 36

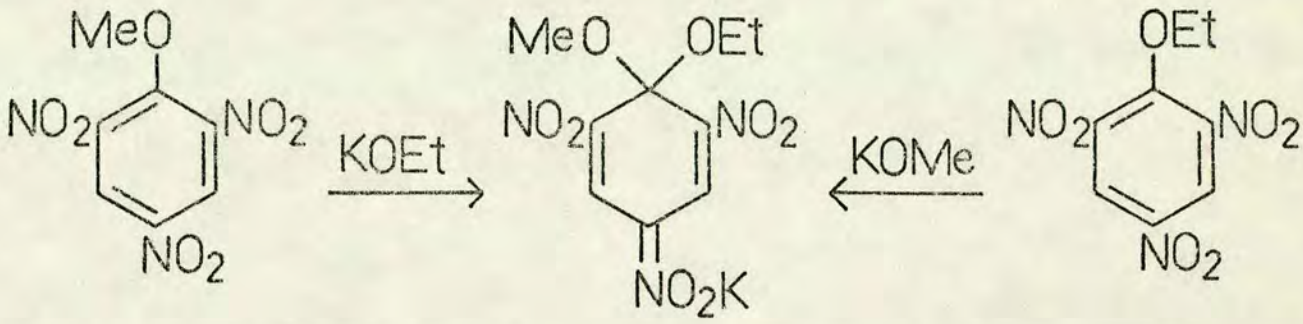

X
NO2
NO2
+
R2NH
k1
k-1
H
+NR2
X
NO2
NO2
k2
-HX
NR2
NO2
NO2
base
k3
fast
-X-
X
NR2
NO2
NO2

Scheme 37

The more powerful the nucleophile the more rapid is the reaction. Substitution is also facilitated by the inclusion of electron-withdrawing substituents in the benzene ring which stabilise the negatively charged (carbanion) intermediate (204). These observations are inconsistent with a unimolecular mechanism which would not involve the nucleophile in the rate-determining step and one requirement for which is electron availability (as opposed to electron deficiency) to stabilise the aryl cation intermediate.

Strong evidence[81] for the addition-elimination mechanism has been obtained from studies of the effect of base-catalysis on the reactions of primary and secondary amines with 2,4-dinitrohalobenzenes. The mechanism (Scheme 37) proposed for this reaction is similar to Scheme 36 but contains a step allowing for transfer of a proton to the base. Application of the steady state approximation to rate calculations for this reaction furnishes results consistent with experimental data. The other main line of evidence in favour of the addition-elimination mechanism is provided by the spectroscopic observation and, in many cases in which the negative charge is delocalised by the presence of electron-withdrawing substituents, the isolation of adducts of the type (204), known as Meisenheimer (or anionic sigma) complexes. It is clearly important to demonstrate that Meisenheimer complexes are true intermediates and are not merely produced in side reactions. The recent upsurge in interest in anionic σ-complexes is related to their probable intermediacy in aromatic nucleophilic substitution reactions and has been made possible by the advent of nuclear magnetic resonance spectroscopy.

Meisenheimer[82] isolated the same red salt by the addition of potassium ethoxide to 2,4,6-trinitroanisole (205) or of potassium methoxide to 2,4,6-trinitrophenetole (206).

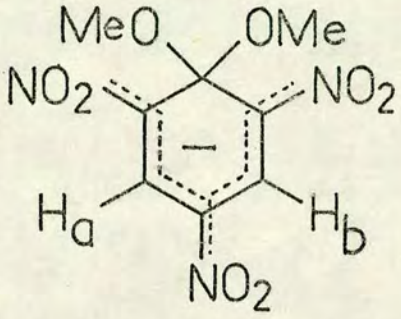


(205) (207) (206)

Since acidification in both cases yielded the same mixture of methyl and ethyl picrate, Meisenheimer proposed the structure (207) for the salt, formed by attack of ethoxide and methoxide at C-1 in the respective substrates (205) and (206).

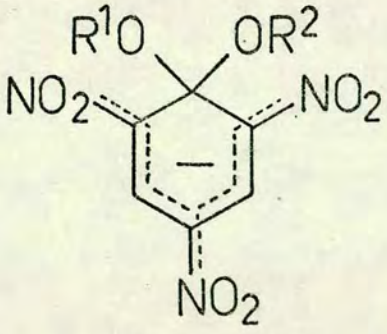
The early research into σ-adducts depended on their isolation and subsequent chemical analysis. Because of the intense colours of Meisenheimer complexes, visible spectroscopy has been employed more recently in the study of their constitution. However apart from absorption ($\lambda_{max.}$ 460 and 500 nm) characteristic of Meisenheimer adducts in general, no specific structural evidence is provided by this property. It was the application of ^{1}H n.m.r. spectroscopy to the problem of Meisenheimer complex structure which demonstrated the accuracy of Meisenheimer's original formulation. The ^{1}H n.m.r. spectrum[83] of 2,4,6-trinitroanisole in dimethyl sulphoxide shows absorptions at τ 0.93 (2H,s,ArH) and

τ 5.93 (3H,s,Me). The Meisenheimer compound (208), in the same solvent, exhibits ^{1}H n.m.r. absorption at τ 1.36 (2H, s,H_a and H_b) and τ 6.97 (6H,s,2 x Me). The single signal



(208)

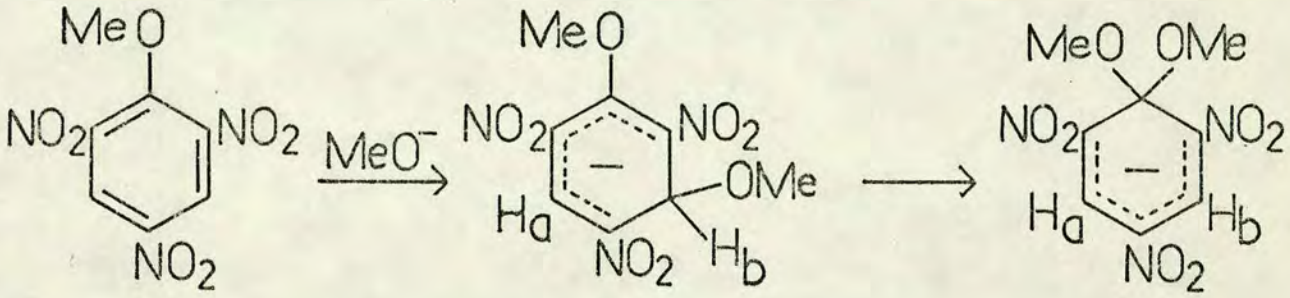
observed for the protons of the methoxyl groups indicates their equivalence and the observed upfield shift is compatible with the change in hybridisation at C_1 from sp^2 to sp^3. The high field signal for the two equivalent ring protons has been explained by Zollinger et al.[84] Thus, whereas the negative charge on the nitro-groups is increased on adduct formation, the electron density in the ring decreases. The increased screening of the ring protons is attributed to a reduction in the ring-current which normally causes a downfield shift in the ^{1}H n.m.r. of aromatic protons.



R^1	R^2
Me	Et
Et	Et

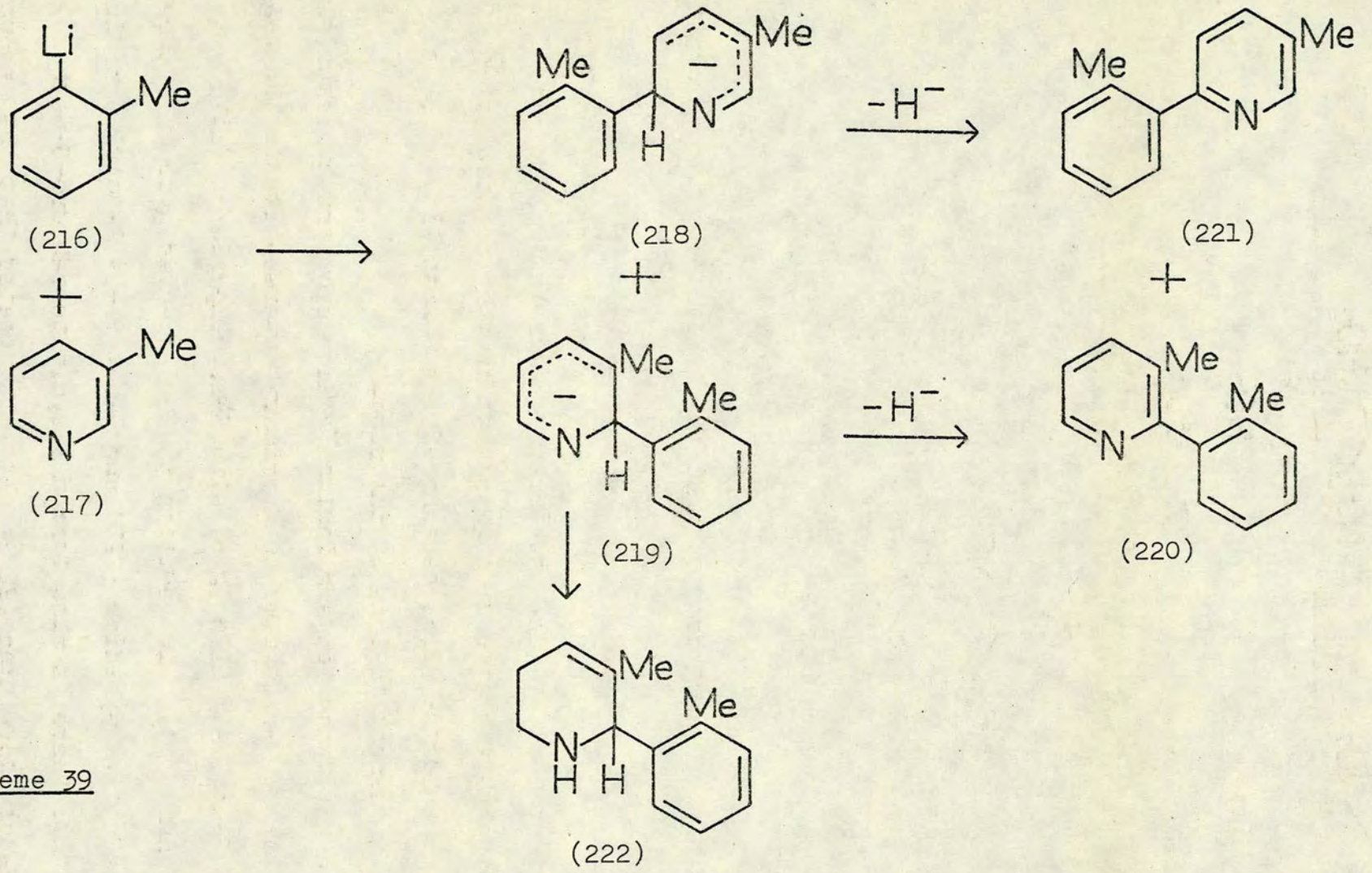
(209)

The structure of other Meisenheimer complexes has been established[83] likewise by ^{1}H n.m.r. spectroscopy to be of the general type (209). In addition, Servis[85] has shown by ^{1}H n.m.r. spectroscopy that when sodium methoxide is added to a solution of 2,4,6-trinitroanisole in dimethyl sulphoxide the initial attack by methoxide ion occurs at the 3-position to form the kinetically favoured adduct (210)

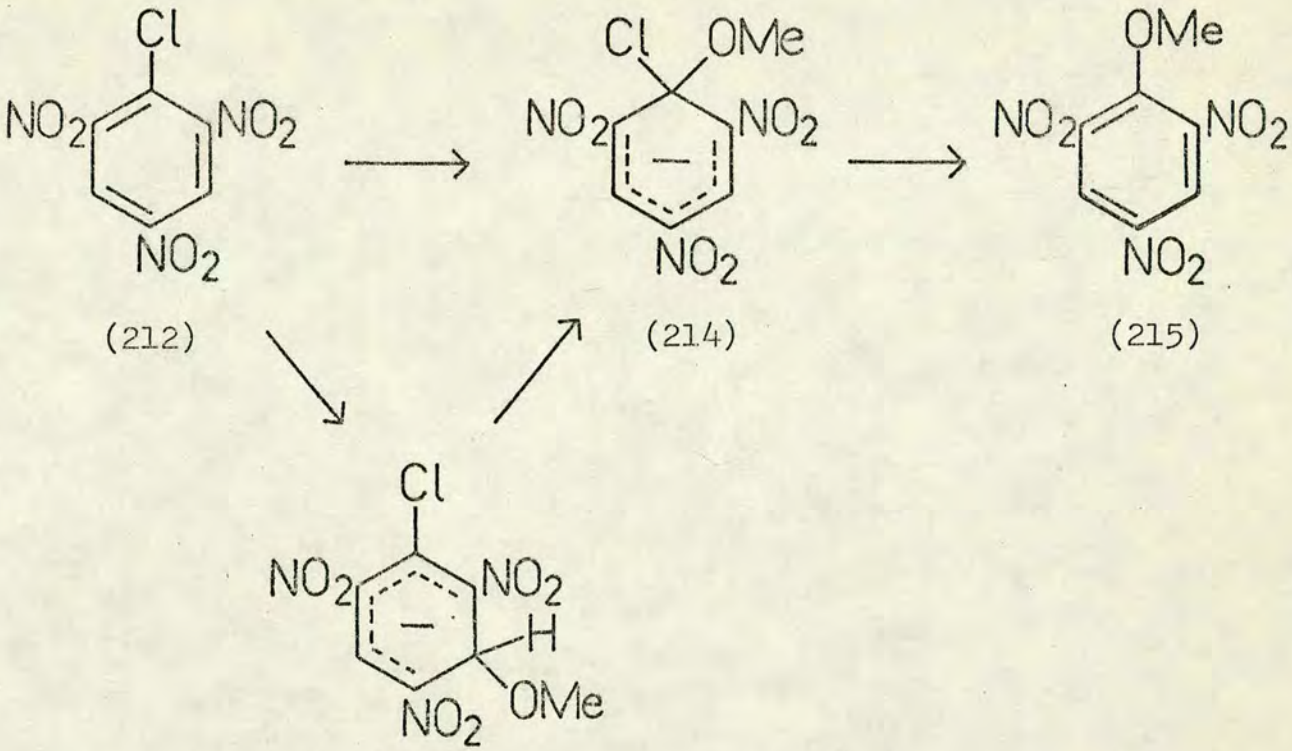


(210) (211)

which is ultimately transformed into the thermodynamically stable adduct (211) having the methoxyl group in the 1-position. Immediately after mixing, the ^{1}H n.m.r. spectrum showed two pairs of doublets (τ 1.58 and 3.83, J 2 Hz) corresponding to H_a and H_b in (210) as well as a singlet, τ 1.36, assigned to the two equivalent ring protons, H_a and H_b in (211). With time the spectrum changed to that of (211) only. The base-catalysed substitution of chlorine in an activated aromatic substrate was thought to follow the usual direct S_N2 mechanism (See Scheme 36, page 44), [(212)→(214)→(215)] (Scheme 38), involving an intermediate (214) of finite stability. Recently Crampton et al.[86] have demonstrated, by


Li
Me
(216)
+
Me
N
(217)
Me
Me
N
H
(218)
+
Me
N
H
Me
(219)
Me
N
H H
(222)
-H⁻
Me
N
(221)
+
Me
Me
N
(220)

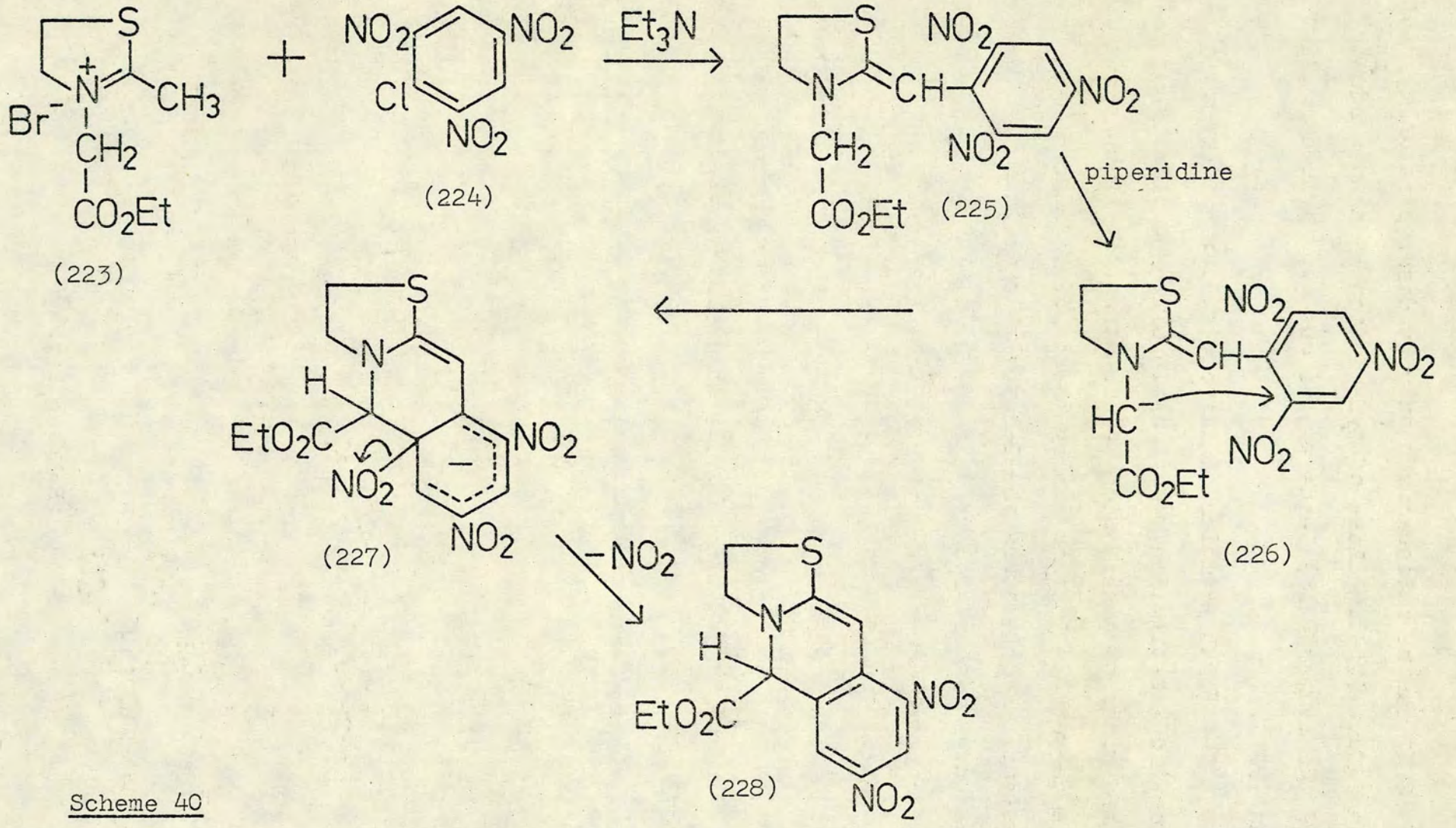
Scheme 39



Scheme 38

^{1}H n.m.r. spectroscopy, that the reaction of the methoxide ion with 2,4,6-trinitrochlorobenzene (212) results in the initial formation of the complex (213). Subsequent rearrangement of (213) to (214) results in nucleophilic substitution affording (215) rather than the isolation of a stable adduct (214) because of the instability of (214) with respect to loss of chlorine.

Abramovitch and Poulton[87] have provided evidence that a Meisenheimer complex is a primary intermediate in the reaction of 2-tolyl-lithium (216) with 3-methylpyridine (217) (Scheme 39). In addition to the expected products, 3-methyl-2-(2-tolyl)pyridine (220) and 5-methyl-2-(2-tolyl)pyridine (221), there is also formed 1,2,5,6-tetrahydro-3-methyl-2-(2-tolyl)pyridine (222). It is suggested that the production

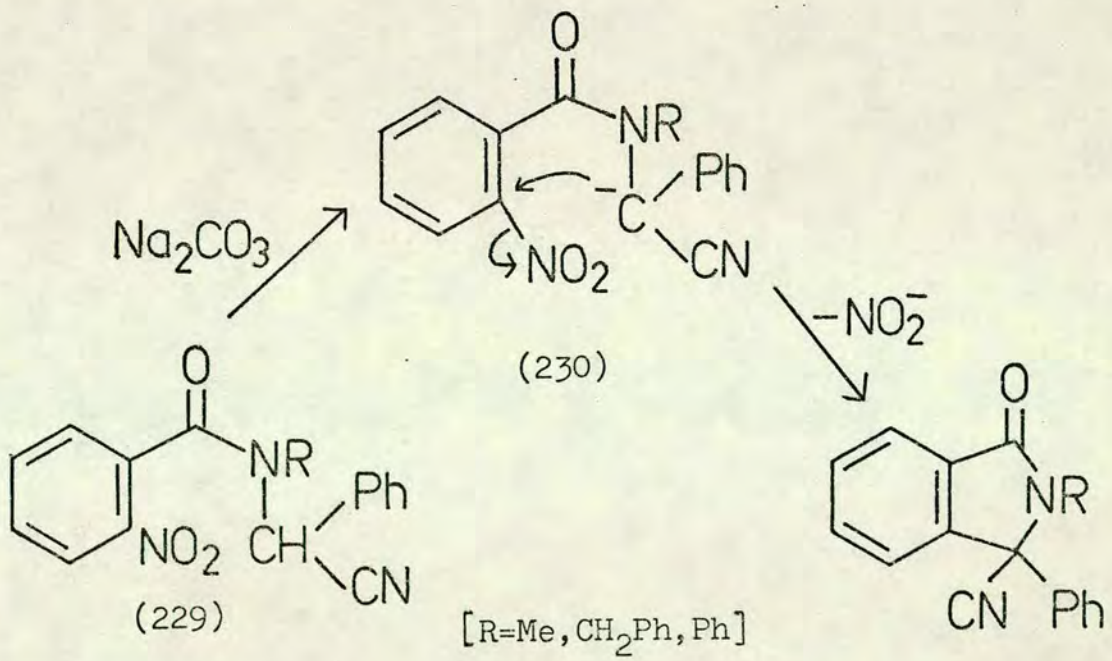

Br⁻
CH3
CH2
CO2Et
(223)
NO2
Cl
NO2
(224)
Et3N
CH
(225)
piperidine
HC⁻
(226)
EtO2C
H
(227)
−NO2
(228)

Scheme 40

of (222) can be rationalised only by disproportionation of the adduct (219). Loss of hydride ion from this adduct and the isomer (218) leads to the observed products (220) and (221).

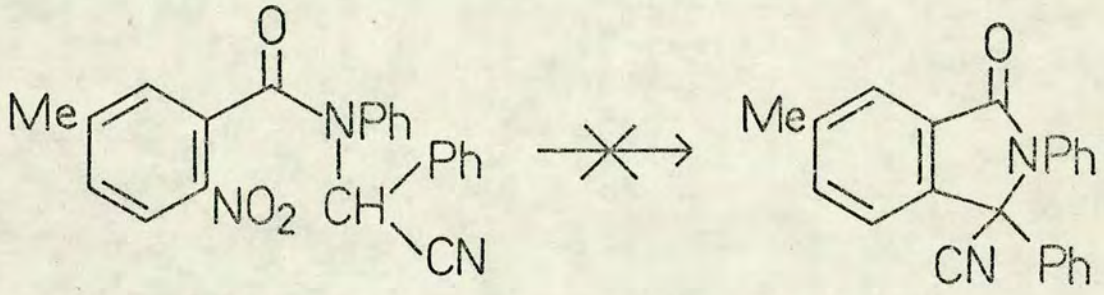
The first examples of intramolecular nucleophilic aromatic substitution reactions involving displacement of a nitro-group by a carbanion were utilised by Krohnke and his co-workers[88,89] in the synthesis of condensed heterocyclic systems. For example the 2-methylthiazolinium bromide (223) condenses with picryl chloride (224) at the 2-methyl group to form the benzylidene thiazolidine (225) (Scheme 40), which then undergoes cyclisation to the thiazoloisoquinoline (228) by nucleophilic displacement of the nitro-group by the acidic N-methylene group, [(225)→(226)→(227)→(228)].

More recently relatively inaccessible isoindolinones (231) have been obtained[90] in high yield by heating N,N-di-substituted 2-nitrobenzamides (229) under reflux in ethanolic sodium carbonate (Scheme 41). This cyclisation is readily



Scheme 41

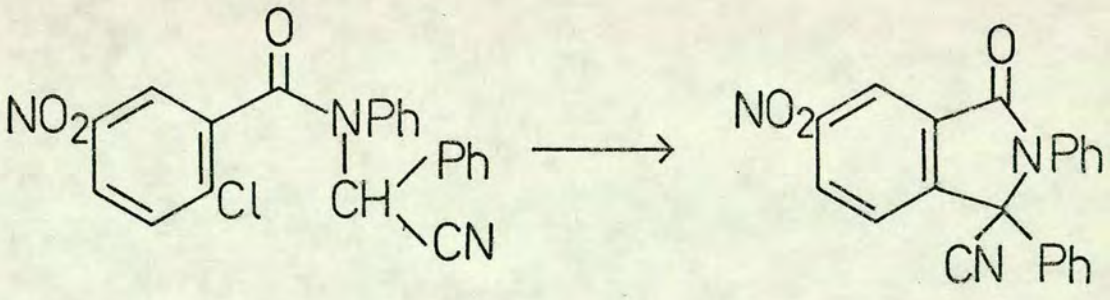
explained in terms of displacement of the nitro-group by the cyanobenzyl carbanion generated in the side-chain [(230)→(231)]. The sensitivity of this reaction to the degree of electron deficiency at the nitro-group is clearly shown by the failure of the amide (232) to undergo cyclisation [(232)→(233)] on treatment with ethanolic sodium carbonate. The effect of the electron-releasing methyl group is, however, overcome by using ethanolic sodium ethoxide as the catalyst



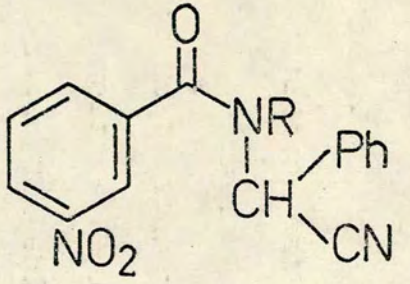
(232) (233)

and smooth ring closure to the methylphthalimidine (233) is then accomplished.[90]

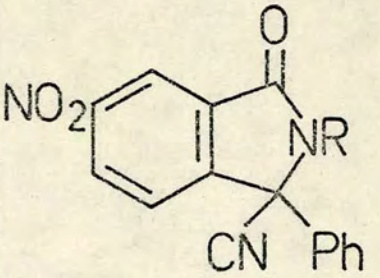
Similar cyclisations involving nucleophilic displacement



(234) (235)

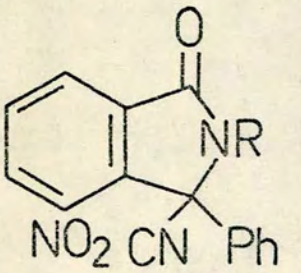


(238)

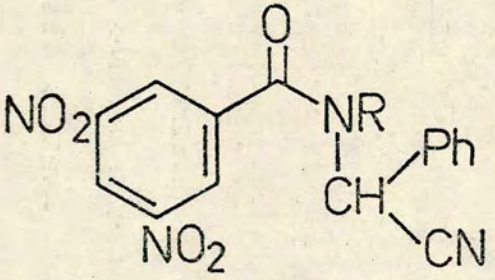


(239)

+



(240)



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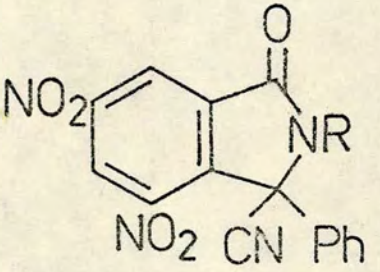


(242)

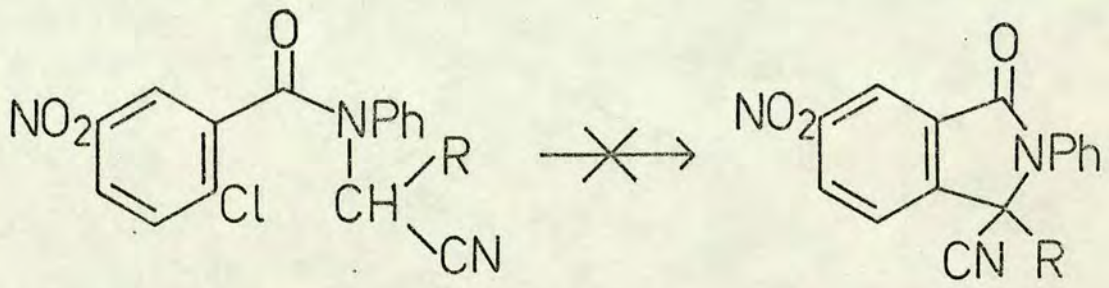
R

a; Ph

b; CH_2Ph

c; Me

of chlorine are also possible as shown by the cyclisation[90] of the amide (234) to the phthalimidine (235), although activation by the presence of the electron-withdrawing nitro-group is necessary. That the stability of the carbanion is important is shown by the lack of reactivity



(236) [R=Me,H] (237)

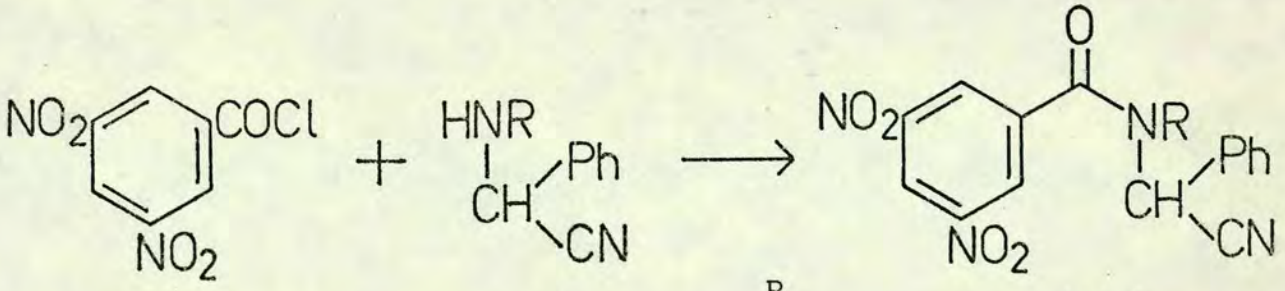
towards cyclisation of the amides (236) in which the side-chain cannot readily stabilise the requisite carbanion centre.

It was considered of interest to study the scope of this type of cyclisation and in particular that of N,N-di-substituted 3-nitro- and 3,5-dinitrobenzamides (238) and (241). Cyclisation of amides of the types (238) and (241) might afford phthalimidines (239), (240) and (242) by intra-molecular nucleophilic displacement of hydride ion. Although rare, the intermolecular nucleophilic displacement of hydride ion in aromatic systems is not unknown (e.g. see page 49 and Scheme 39). In contrast, only one example of an intra-molecular nucleophilic aromatic substitution reaction involving the formal displacement of hydride ion appears to have been reported. Heating the meta-nitrobenzamide (238a) in ethanolic sodium carbonate was shown[91] to afford in low

yield a mixture which was separated by chromatography to give mainly the 5-nitroisoindoline (239a) together with the 7-nitro isomer (240a). The mechanism of this reaction can be considered analogous to that shown in Scheme 41 but involving substitution of hydrogen. The formation of the isomers (239a) and (240a) indicates competing attack by the cyanobenzyl carbanion ortho and para to the nitro-group. This and related cyclisations have now been further studied to gain evidence as to their scope.

As an initial approach to the study of cyclisations which might proceed by displacement of hydride ion it was decided to investigate the dinitroamides (241a-c). These molecules have two distinct advantages over their mono-nitro analogues (238a-c). In the first place successful cyclisation in the symmetrical structures (241) should lead to a single product in contrast to potential isomer formation in the cyclisation of the mono-nitroamides (238). Secondly the greater electron deficiency of the benzene ring in the dinitroamides (241) should render nucleophilic displacement of hydride ion more favourable.

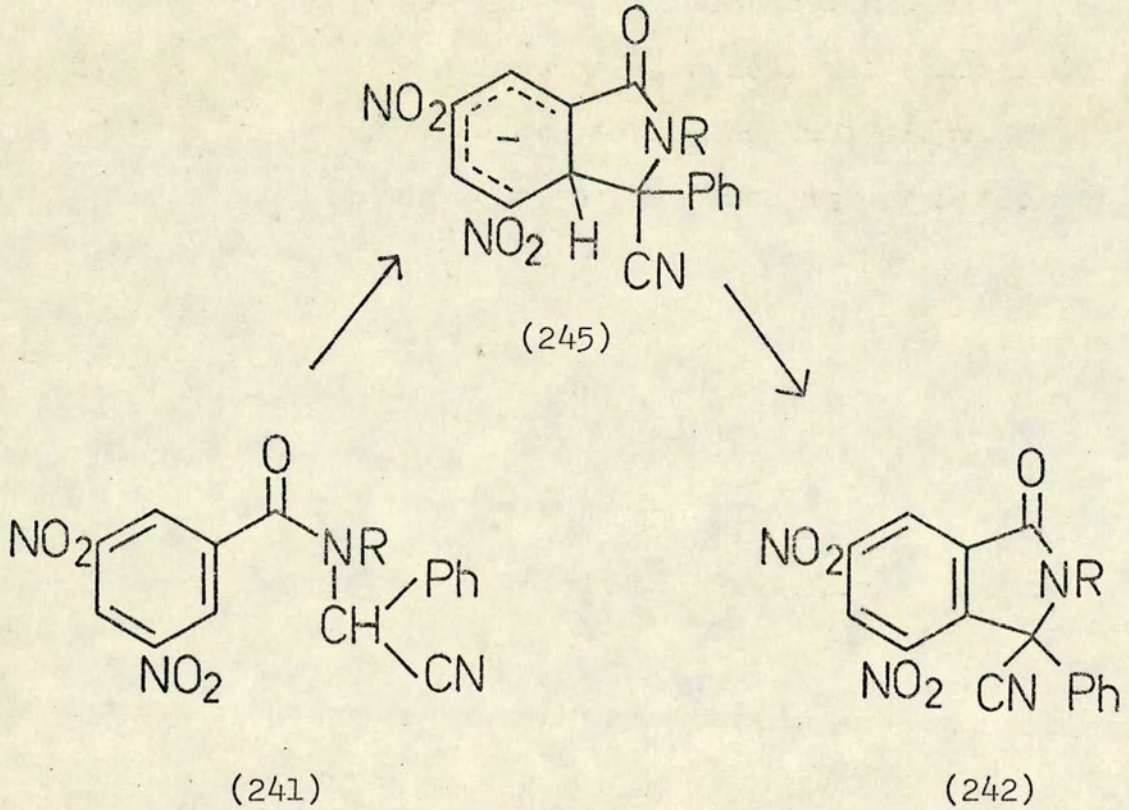
The dinitroamides (241a-c) were prepared in excellent



(243) (244)

R
a; Ph
b; Ch_2Ph
c; Me

(241)



R

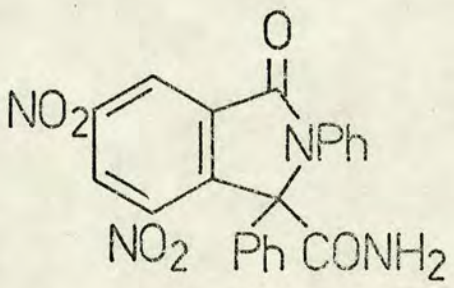
a; Ph

b; CH_2Ph

c; Me

yield by condensing the acid chloride (243) in benzene with two molar equivalents of the appropriate readily available N-substituted aminophenylacetonitriles (244a-c). The elemental analyses and spectroscopic properties of the products were in accord with the amide structures (241).

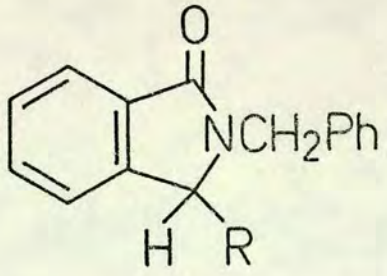
The dinitrobenzamide (241a), on stirring at room temperature for 1.5h with ethanolic sodium carbonate, gave an unresolvable four component mixture whose i.r. spectrum indicated the presence of the expected product (242a) together with the amide (246) derived by hydrolysis of (242a).



(246)

Since this result suggests side-reactions caused by an over-basic reaction medium the attempted cyclisation was repeated using sodium acetate as the catalyst. Under these conditions the phthalimidine (242a) was formed in moderate yield (62%). Heating the dinitroamide (241b) under reflux in ethanolic sodium acetate gave a mixture from which the phthalimidine (242b) was also isolated in moderate yield. The lower yields in these cyclisations which involve the formal displacement of hydride ion, compared to that obtained[90] in the cyclisation of the chloroamide (234) may be partly due

to side-reactions involving reduction either by hydride ion or a readily oxidised intermediate [e.g. (245)]. In accord with these suggestions the sodium acetate catalysed cyclisations of the amides (241a-c) in the presence of para-benzoquinone gave the dinitrophthalimidines (242a-c) in much improved yield (>90%). The function of the mild oxidising agent, para-benzoquinone, is presumably either to scavenge liberated hydride ion, or to oxidise the intermediate (245) to the stable end-product (242). The dinitrophthalimidines (242a-c) gave correct analytical and mass spectral data and their i.r. spectra contained bands characteristic of a nitro-group and the carbonyl group of a ring-fused γ-lactam. The substitution pattern in the phthalimidines (242a-c) was confirmed by their ^{1}H n.m.r. spectra which showed two low field meta-coupled protons. In the case of the phthalimidine (242b) the ^{1}H n.m.r. absorption of the benzyl protons appears as a pair of doublets (τ 4.72 and 5.66) indicating restricted rotation of the benzyl group about the C-N bond. Similar multiplicity in the ^{1}H n.m.r. spectrum of the isoindolinones (247)[92] is likewise attributed to hindered rotation in the N-benzyl substituent.

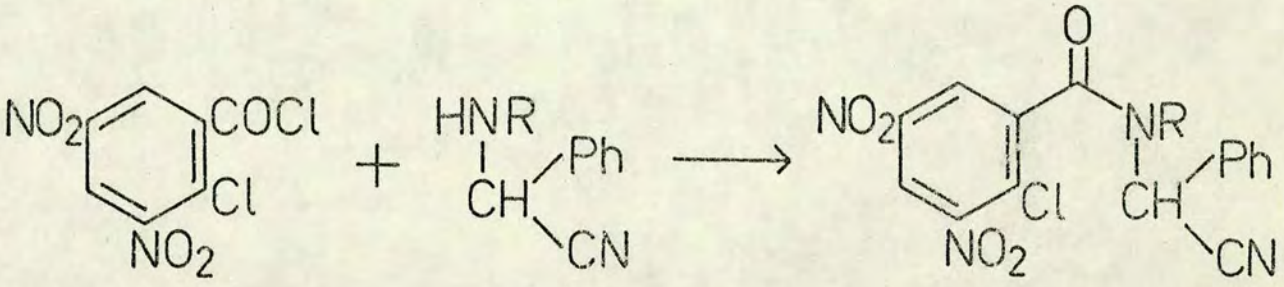


(247)

[R=Me,Ph]

N-Bromosuccinimide has been used[93] to oxidise Meisenheimer adducts but an attempt to cyclise the amide (241a) in the presence of N-bromosuccinimide resulted only in the recovery of the starting amide (241a).

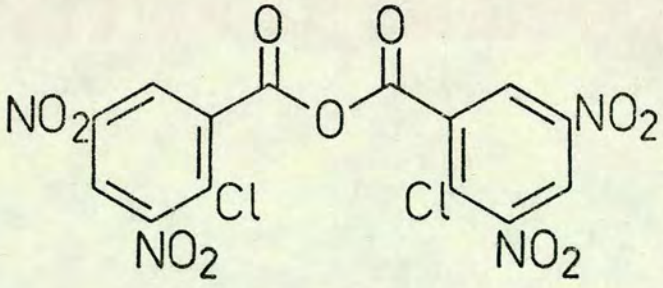
As further support for the structures of the phthalimidines (242a-c) and to extend the cyclisation [(234)→(235)] of the chloroamide (234) the cyclisations of the dinitrochloroamides (249a-c) were studied.



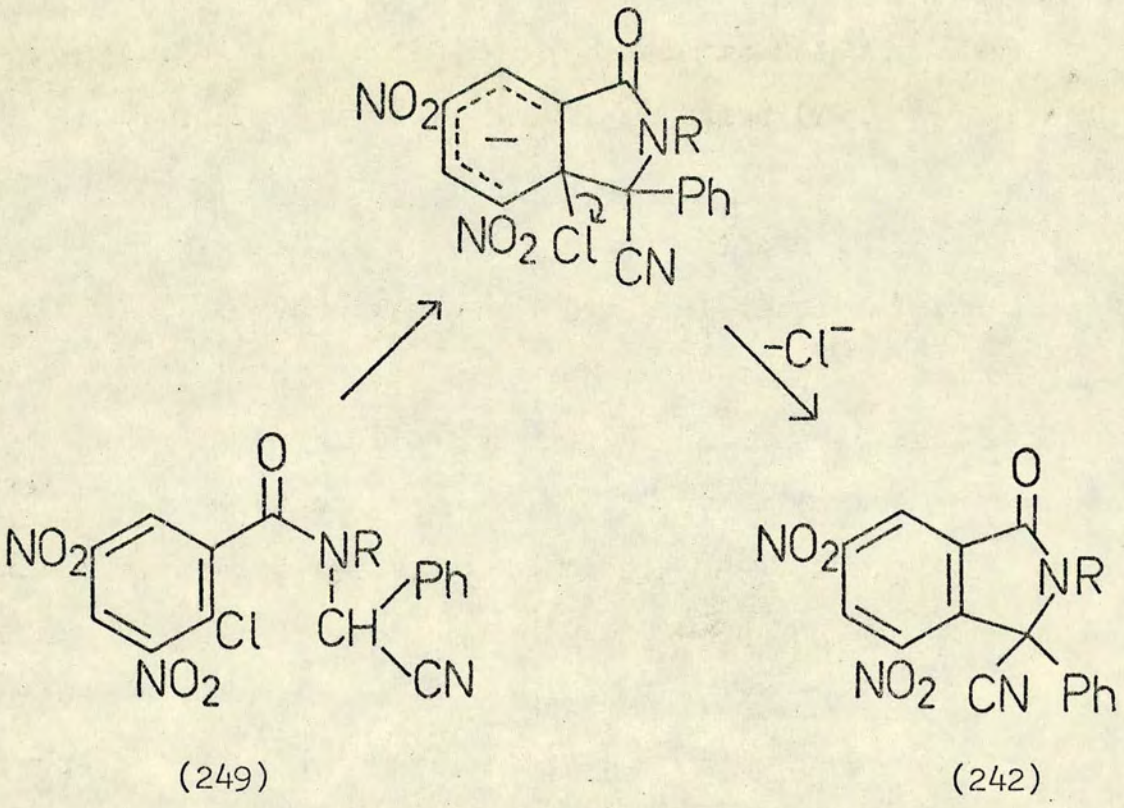
(248) (244) (249)

R
a; Ph
b; CH_2Ph
c; Me

In the synthesis of the acid chloride (248) from 2-chloro-3,5-dinitrobenzoic acid,[94] as well as the expected product, a highly insoluble solid was isolated. This was



(250)



(249) (242)

R

a; Ph

b; CH_2Ph

c; Me

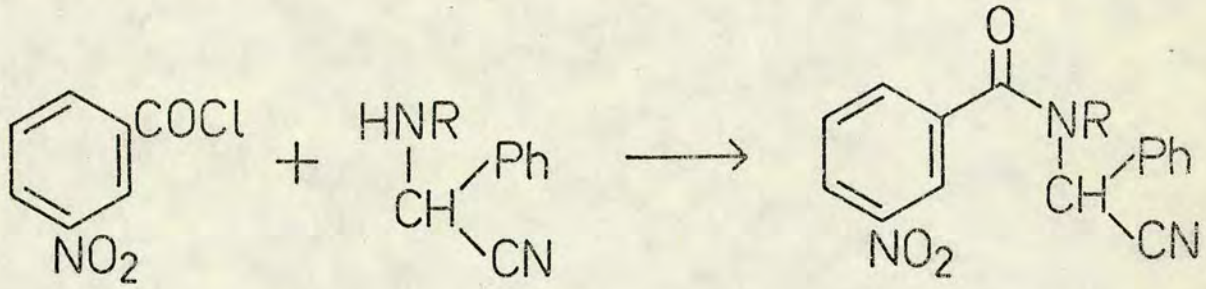
identified as 2-chloro-3,5-dinitrobenzoic anhydride (250) on the basis of its elemental and mass spectral analysis and its i.r. spectrum which showed absorption bands at 1780 and 1740 cm^{-1}, characteristic of acyclic carboxylic acid anhydrides. The dinitrobenzamides (249a-c) were readily prepared by the condensation of the acid chloride (248) with the N-substituted aminophenylacetonitriles (244), the structures (249) being confirmed by their spectroscopic properties.

The dinitrochloroamide (249a) when heated under reflux for 1 h with ethanolic sodium carbonate gave an unresolvable five component mixture. When the reaction time was reduced to two minutes the pure dinitrophthalimidine (242a) was isolated in moderate yield (48%) by extracting the three component mixture with ethanol. Similar brief (five minutes) treatment of the amide (249b) with ethanolic sodium carbonate gave a mixture of four components from which the phthalimidine (242b) was isolated in low yield (13%) by chromatography.

In view of the relatively complex nature of the sodium carbonate catalysed reactions of the chloro-dinitroamides (249a-c) it was decided to attempt cyclisation using a weaker base in the hope of reducing or eliminating side-reactions leading to mixtures. This turned out to be the case. Thus, brief treatment of the dinitroamides (249a-c) with hot ethanolic sodium acetate resulted in smooth cyclisation in much improved yield (70-95%) to the dinitrophthalimidines (242a-c). The cyclisation products of the chloro-dinitroamides (249a-c) were identical in all respects to the phthalimidines (242a-c) obtained from the dinitroamides (241a-c).

The cyclisation of the amides (249b and 249c) to the phthalimidines (242b and c) was also efficiently carried out by the even weaker base, aniline. It might have been expected that there would be competition by the aniline in the displacement of the chlorine atom from the highly activated substrates (249b and c) but in fact this was not observed, and the expected phthalimidines (242b and c) were formed in high yield (ca. 80%).

To further the investigation of processes involving cyclisation by intramolecular nucleophilic displacement of



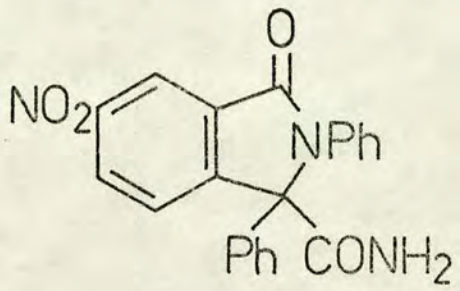
(251) (244) (238)

R
a; Ph
b; CH_2Ph
c; Me

hydride ion the mono-nitroamides (238) were synthesised by condensing 3-nitrobenzoyl chloride with the appropriate amino-compound (244).

In the hope of minimising side-reactions the attempted cyclisation of the mono-nitrobenzamide (238a) was carried out at room temperature in ethanolic sodium acetate. However these conditions proved to be too mild and the starting material was recovered in almost quantitative yield. When the amide (238a) was heated under reflux in ethanolic sodium

acetate a three component mixture was isolated, chromatography of which afforded the 5-nitrophthalimidine (239a)(26%) and the isomeric 7-nitrophthalimidine (240a)(2%). The third component was not isolated but on the assumption that it was the amide (252) derived by hydrolysis of the cyano function in

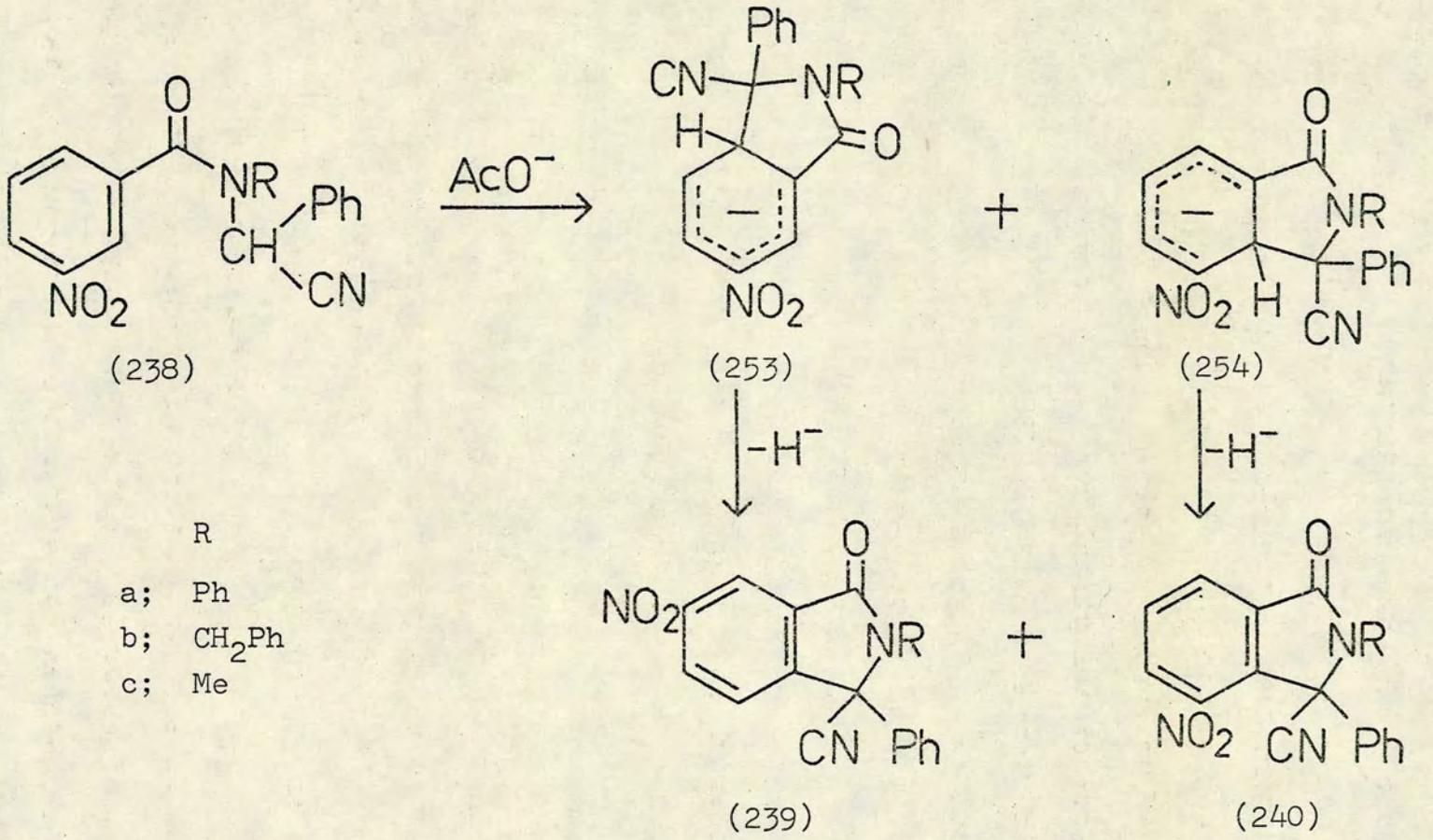


(252)

the phthalimidine (239a) an attempt was made to prepare it. However, heating the phthalimidine (239a) under reflux with ethanolic sodium carbonate for 2h gave an unresolvable mixture of three components, while attempted hydrolysis using aqueous sulphuric acid gave a quantitative recovery of the cyanophthalimidine (239a). It has been demonstrated[95] that hydrolysis of nitriles can be effected by heating at 100° with an excess of polyphosphoric acid, but these conditions applied to the cyanophthalimidine (239a) produced a multi-component mixture.

Since the amide (252) proved to be inaccessible it seemed that it would be simpler to attempt to prevent amide formation during cyclisation. Thus, the mono-nitrobenzamide (238b) was briefly heated under reflux with ethanolic sodium acetate in the presence of para-benzoquinone and in this case t.l.c. showed the presence of only two components in the product.

The mixture was eventually separated after repeated wet-



(238)

(253)

(254)

(239)

(240)

R

a; Ph

b; CH_2Ph

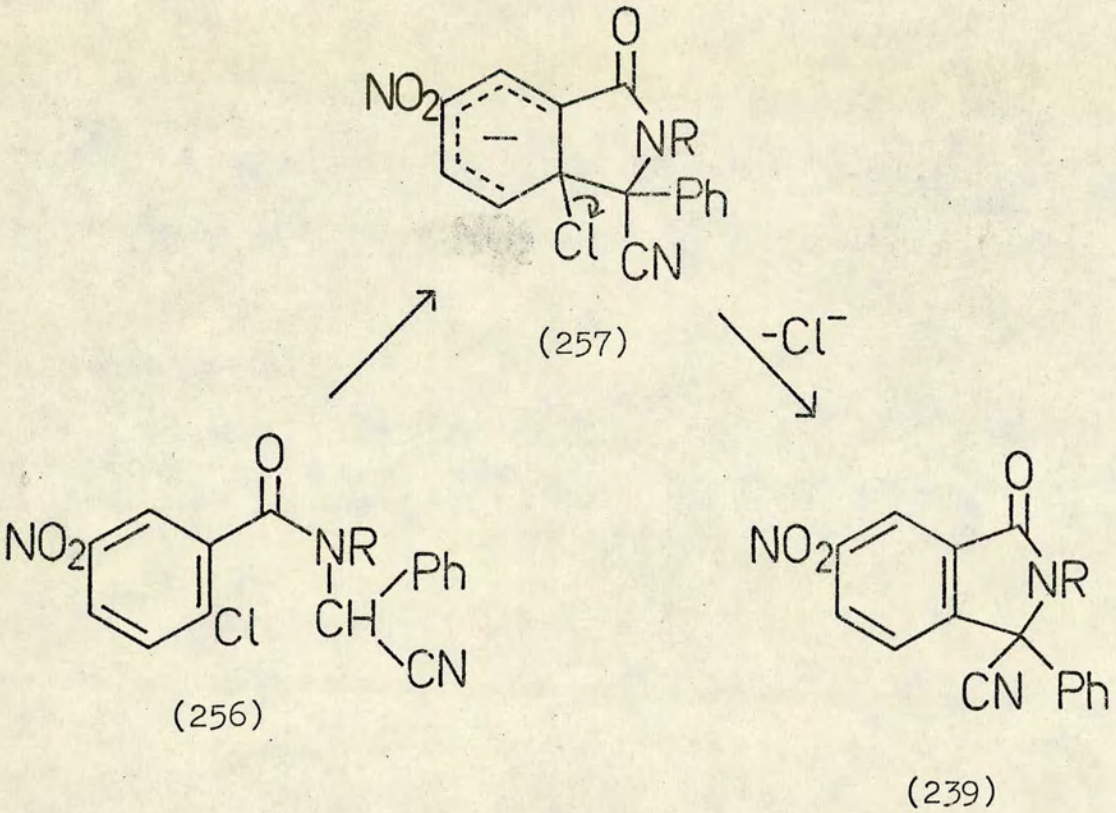
c; Me

Scheme 42

column chromatography, to give the 5-nitrophthalimidine (239b)(65%) and the 7-nitro isomer (240b)(8%). The same cyclisation conditions applied to the mono-nitroamide (238c) again gave a two component mixture. Wet-column chromatography and dry-column chromatography failed to effect a complete separation of the mixture which was finally resolved by high speed liquid chromatography yielding the 5-nitrophthalimidine (239c) and its 7-nitro isomer (240c).

Correct analytical and mass spectral data were obtained for these mono-nitrophthalimidine products,(239b and c) and (240b and c), with the exception that (240c) did not give a satisfactory elemental analysis. The structure of these products is argued by analogy with the known[91] mono-nitrophthalimidines (239a) and (240a) and on the basis of their i.r. spectra which contained absorption bands attributable to a nitro-group and the carbonyl group of a γ-lactam. The splitting pattern of aromatic protons in their ^{1}H n.m.r. spectra confirmed the respective 5- and 7-positions for the nitro-groups in the phthalimidines (239b and c) and (240b and c). Again, multiplicity in the ^{1}H n.m.r. absorption of the benzyl protons in both (239b) and (240b) indicates restricted rotation in the benzyl group.

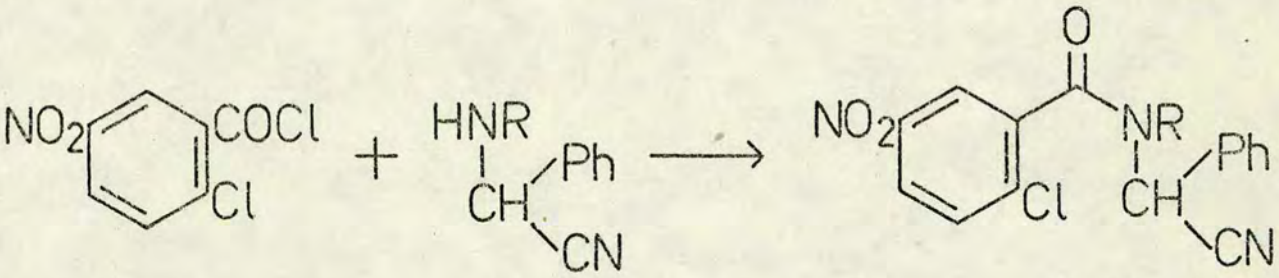
The relative yields of the two isomers (239) and (240) obtained in the cyclisations of the amides (238) is readily explained (Scheme 42). The cyanobenzyl carbanion generated in the side-chain can attack the benzene ring at two non-equivalent positions forming intermediates (253) and (254). Due to steric hindrance caused by the adjacent nitro-group



	R
a;	Ph
b;	CH_2Ph
c;	Me

the formation of (254) is opposed relative to (253) and consequently the yield of phthalimidine (240) would be expected to be less than that of (239). The striking feature of the cyclisations of the amides (238a-c) is the remarkable ease with which hydride ion is displaced, the reactions being carried out under mildly basic conditions.

Further evidence for the structures of the 5-nitrophthalimidines (239) was provided by the cyclisations of the chloroamides (256). These amides (256a-c), prepared by condensing the acid chloride (255) with the amino-compound (244), were



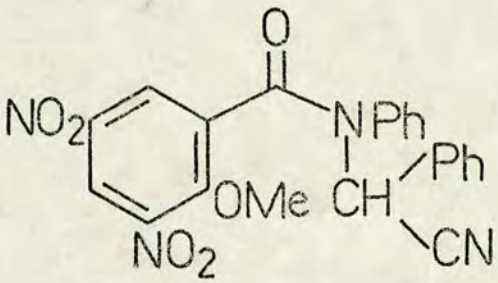
(255) (244) (256)

R
a; Ph
b; CH_2Ph
c; Me

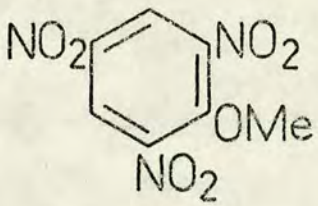
heated under reflux in ethanolic sodium carbonate. The immediate red colour that developed, which may be indicative of the formation of an intermediate Meisenheimer-type complex (257) since they are known to be highly coloured species, was in two cases (256a and b) discharged within two minutes. Inferring that this was a sign of the conversion of the intermediate to product, the mixtures were worked up to give high yields of the 5-nitrophthalimidines (239a and b). However in the case of the amide (256c) the red colour persisted but,

despite this, work up after heating for 1h gave an excellent yield (90%) of the phthalimidine (239c). The products obtained in these reactions by displacement of chloride ion are identical to the compounds assigned the 5-nitrophthalimidine structures from the cyclisations of the mono-nitroamides (238).

Since many Meisenheimer complexes have been detected by spectroscopy and the more stable adducts isolated, it was of considerable interest to try to detect the intermediates in the cyclisations leading to phthalimidines. The amide (258)



(258)



(259)

was selected for study because clearly it is closely related to 2,4,6-trinitroanisole (259), the subject of many such investigations.[96,97] It was felt that results obtained with the amide (258) would be more easily rationalised in the light of the known behaviour of 2,4,6-trinitroanisole (259).

Condensation of the acid chloride (260) with N-phenyl-α-aminophenylacetonitrile (244a) afforded the amide (258) in good yield. A solution of the amide (258) in dimethyl sulphoxide, to which a few drops of triethylamine had been added, had the characteristic red colour associated with Meisenheimer adducts, and the visible spectrum contained

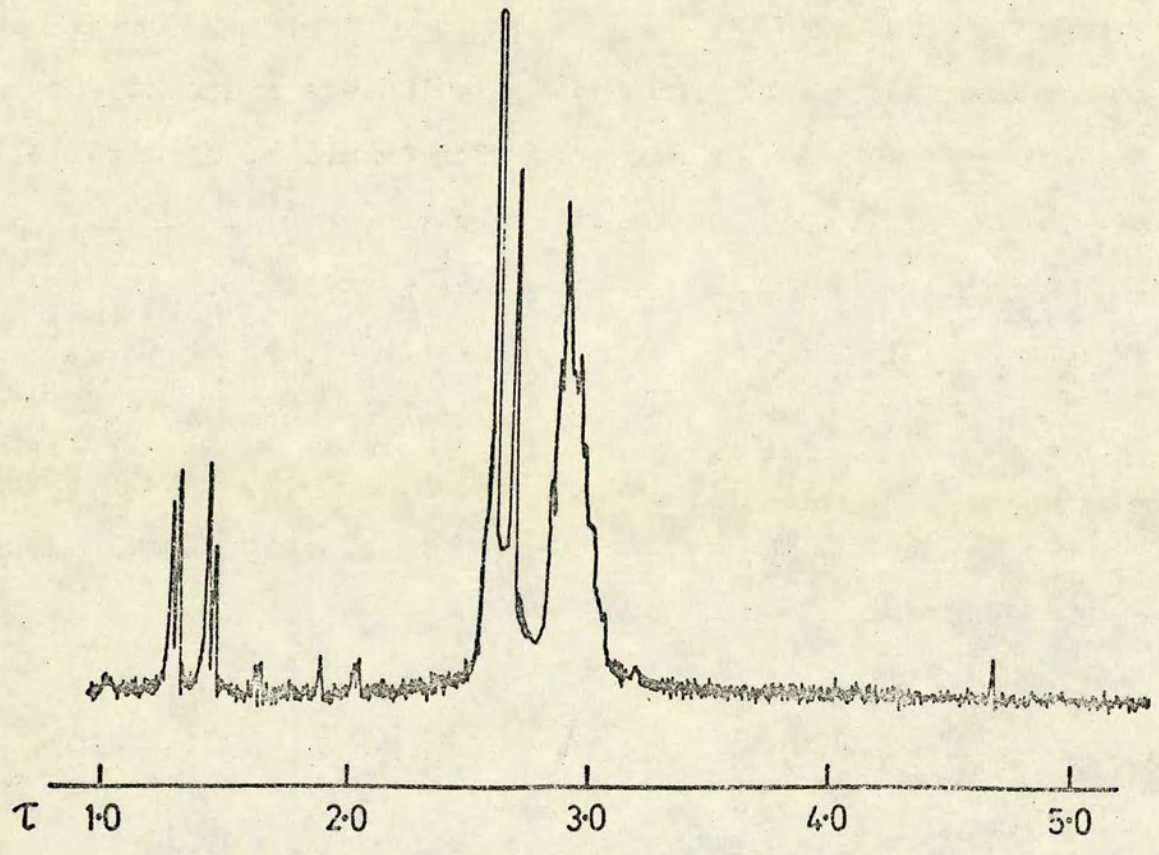
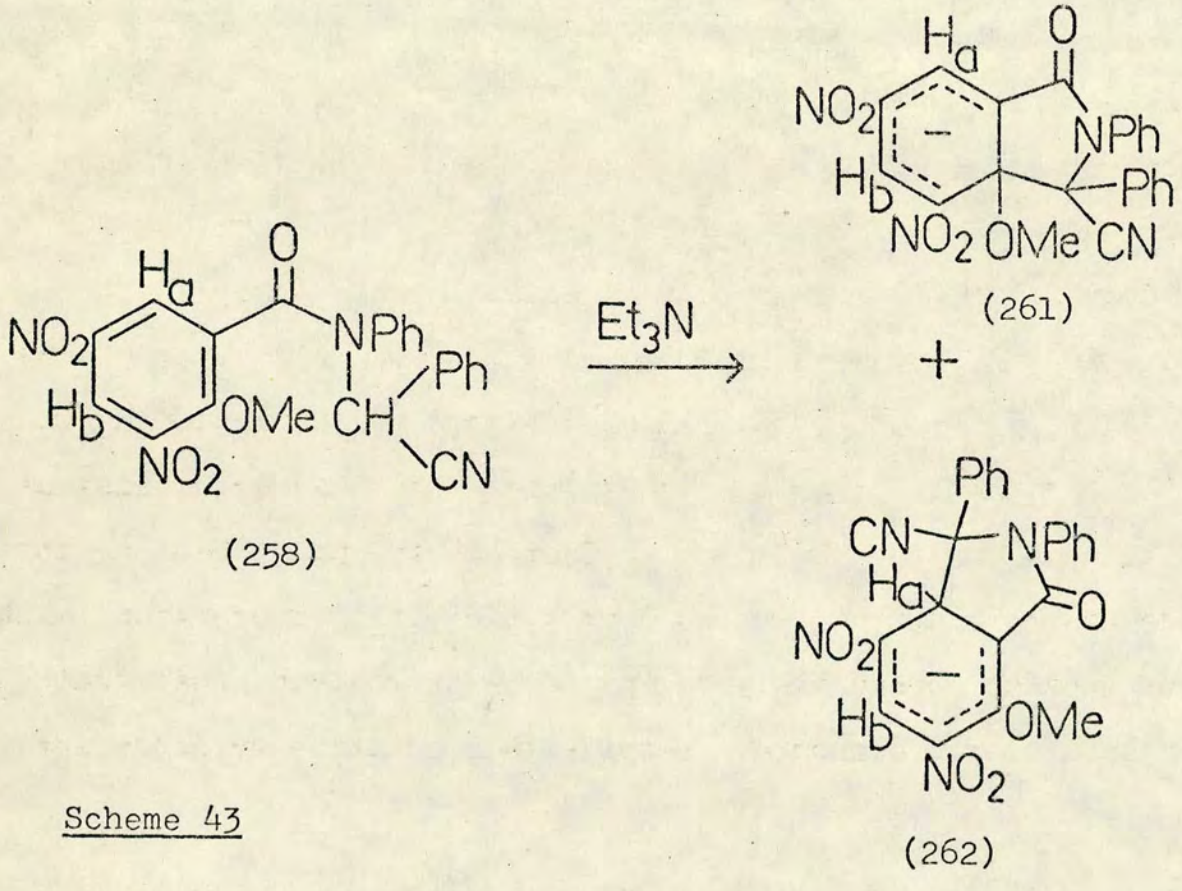
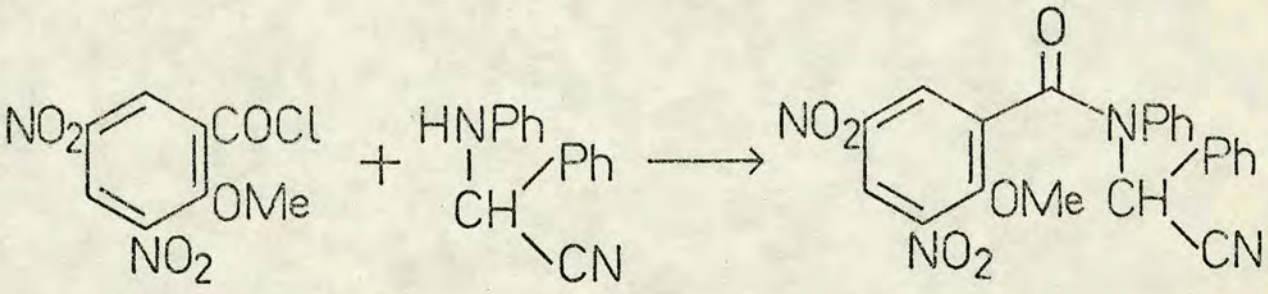


Figure 1



Scheme 43

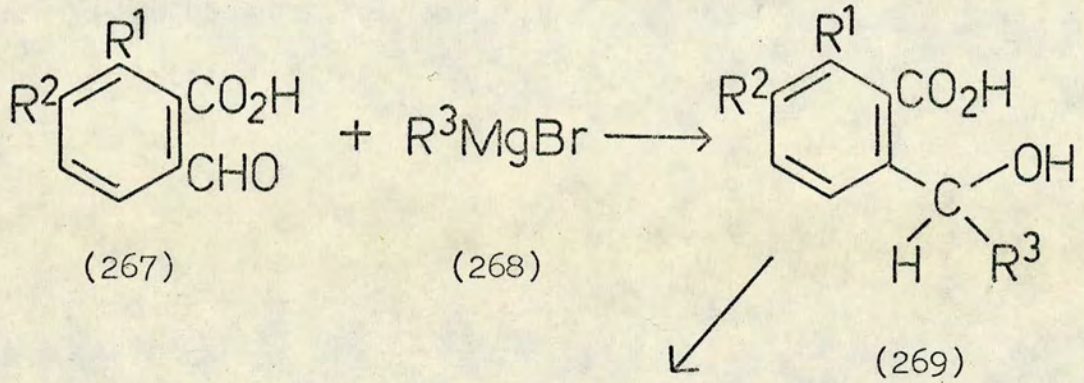
absorptions ($\lambda_{max.}$ 400 and 505 nm) which are indicative of the presence of such an adduct. The ^{1}H n.m.r. spectrum of the amide (258) recorded immediately in [$^{2}H_{6}$] dimethyl sulphoxide containing 0.3 equivalents of triethylamine is illustrated in Figure 1 and can be rationalised as shown in Scheme 43, a situation analogous to that involving the reaction of 2,4,6-trinitroanisole with methoxide ion[85] (cf. page 48). The spectrum shows a pair of <u>meta</u>-coupled doublets



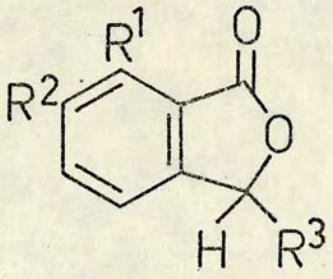
(260) (244a) (258)

at τ 1.24 and τ 1.41 attributable to the ring protons H_a and H_b in unreacted starting amide (258). The pair of doublets centred at τ 1.59 and τ 1.99 are assigned to the two ring protons in (261), the upfield shift being caused by a reduction in the aromatic ring current[84] (cf. page 47). The ring proton H_b in (262) accounts for the signal at τ 1.84 and the signal at τ 4.64 can be assigned to the proton H_a in (262). The large upfield shift of H_a in (262) is consistent with a change in hybridisation from sp^2 to sp^3 at C-6, so that the absorption of H_a in (262) at τ 4.64 is at a position which corresponds more closely to that of a cycloalkane than that of an aromatic compound. Despite this positive evidence for

the formation of the unique Meisenheimer complexes (261) and (262) more detailed investigations will be required before these structures are established conclusively.



(267) (268) (269)



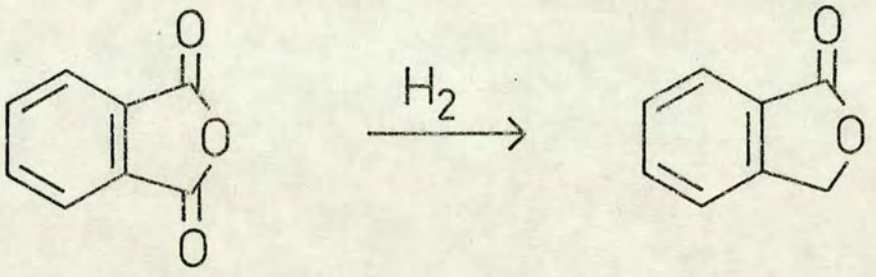
(270)

	R^1	R^2	R^3
a;	H	H	Me
b;	OMe	OMe	Me
c;	H	H	Et
d;	H	H	Ph

Scheme 44

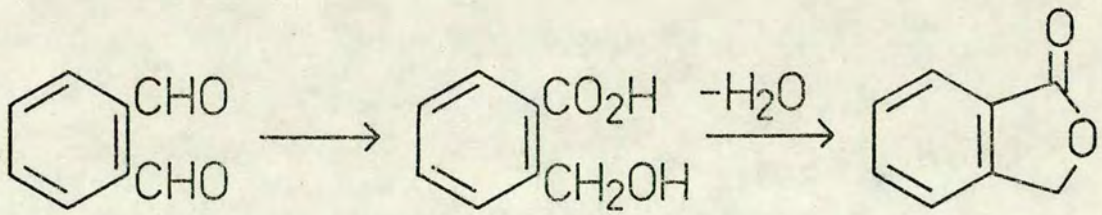
2.3. The Attempted Base-Catalysed Cyclisation of Mandelonitrile 2-Chloro-3,5-dinitrobenzoate

Syntheses of phthalides fall into two general classes. The first, exemplified by the catalytic reduction[98] of phthalic anhydride (263) to the parent phthalide (264), involves modification of an available heterocyclic nucleus.



(263) (264)

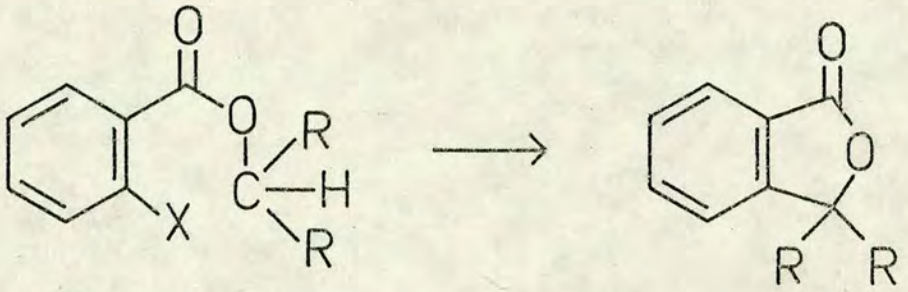
The second and more important method involves the cyclisation of ortho-disubstituted benzene derivatives. The intramolecular Cannizzaro reaction[99] of phthalaldehyde (265) produces 2-carboxybenzyl alcohol (266), which cyclises in the reaction medium to afford phthalide (264). Substituted



(265) (266) (264)

phthalides (270) result[100,101] from the controlled reaction of Grignard reagents (268) with phthalaldehydic acids (267), proceeding through the secondary alcohol (269) which lactonises to yield the product (270) (Scheme 44).

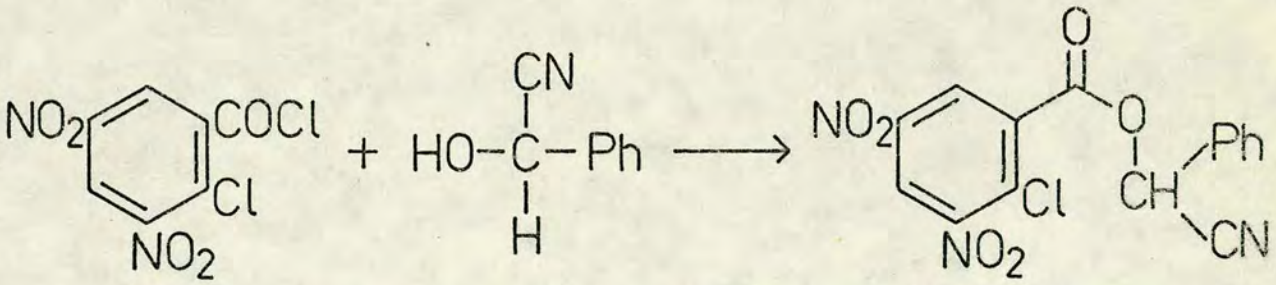
There does not, however, appear to be any report of phthalide formation from a substrate, of the type (271), containing the ester function preformed in a side-chain which



(271) (272)

then cyclises by intramolecular nucleophilic substitution to yield (272). It was realised that since the precursor (271) was closely related to the amides used in the phthalimidine preparations, this approach to phthalide synthesis was worthy of investigation.

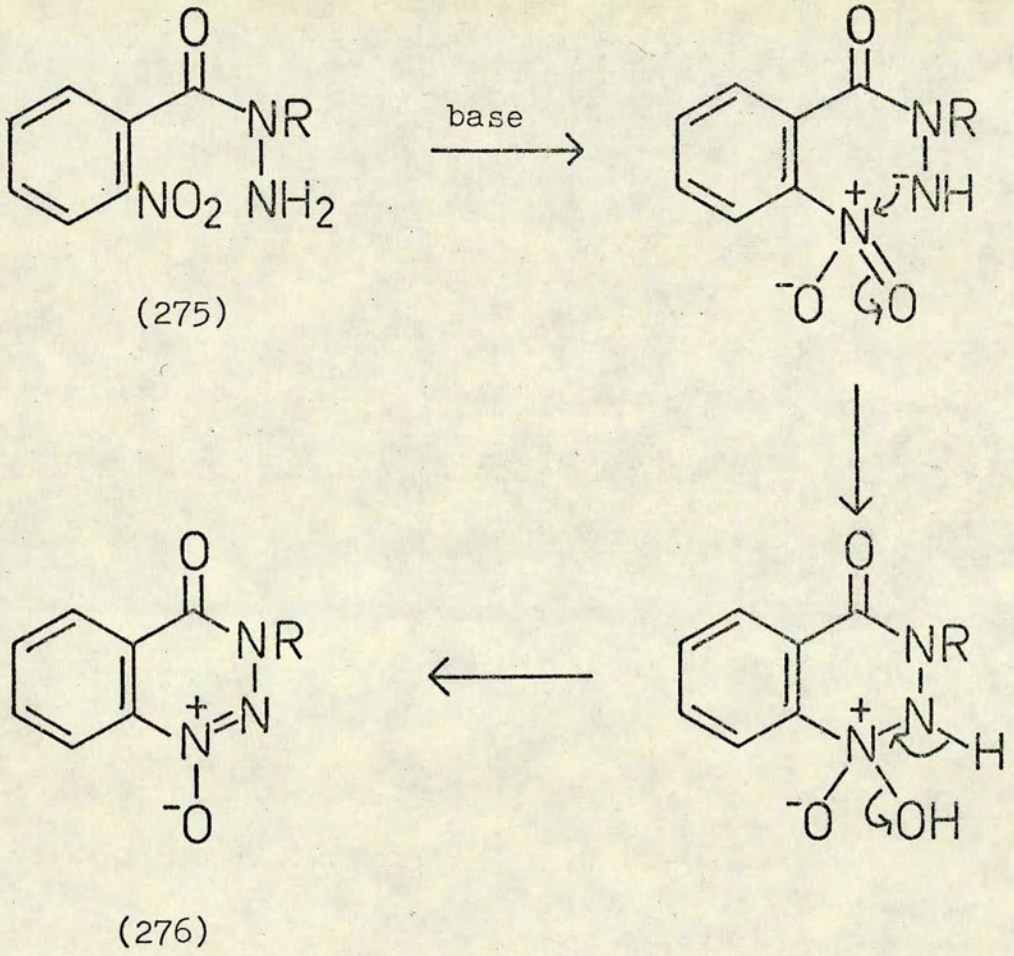
The formation of α-cyanobenzyl 2-chloro-3,5-dinitrobenzoate (274) was readily achieved by condensation of the acid



(248) (273) (274)

chloride (248) with benzaldehyde cyanohydrin (273). However brief heating of the ester (274) under reflux with ethanolic sodium acetate - the conditions applied successfully in the

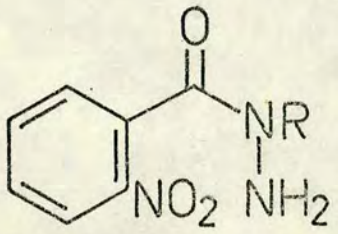
preparations of the phthalimidines - afforded only a multi-component mixture. The complexity of this reaction is probably due to hydrolysis of the substrate (274) and partial cyclisation. The normal relative stability of benzoates to hydrolysis would certainly be reduced by the presence of the electron-withdrawing nitro-groups in the benzene ring.



Scheme 45

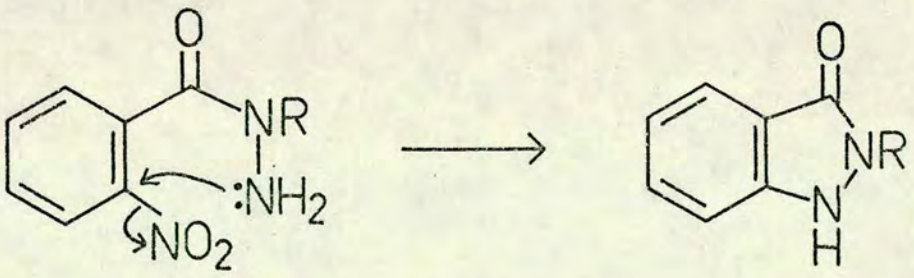
2.4 The Attempted Base-Catalysed Cyclisation of 2-Nitrobenzoylhydrazines

It was also of interest to investigate a further variant of the ortho-nitrobenzamide-type cyclisation; namely that involving 2-nitrobenzoylhydrazines (275). Of the two possible



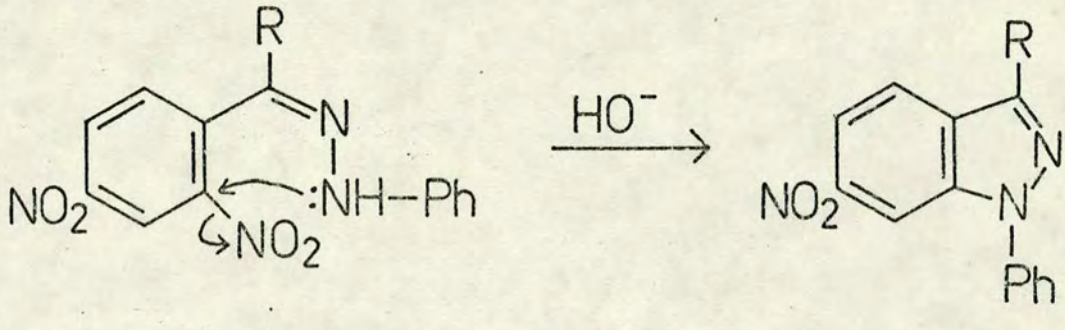
(275)

modes of reaction of such a compound under basic conditions the first (Scheme 45) would lead to the hitherto unknown benzo-1,2,3-triazin-4(1H)-one 1-N-oxides (276). The course indicated is analogous to that suggested for the formation of benzo-1,2,4-triazines (87a) from 2-nitrophenylguanidines (86a) (Scheme 17, page 20), by the base-catalysed aldol-type condensation between an amino and a nitro-group. Alternatively intramolecular nucleophilic displacement of the nitro-group in (275) by the amino-group would afford a 2-substituted



(275) (277)

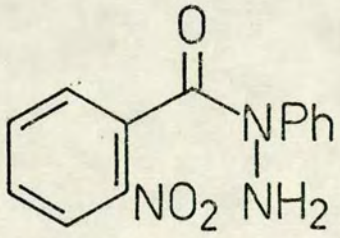
indazolone (277). Such a reaction has precedent in the formation[102,103] of 1-arylindazoles (279) by the base-



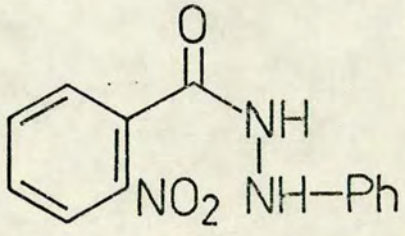
(278) [R=COMe, CO_2Me] (279)

catalysed cyclisation of the dinitrobenzylidenearylhydrazones (278) involving nucleophilic displacement of an aromatic nitro-group.

The hydrazide (280) cannot be prepared by direct reaction of ortho-nitrobenzoyl chloride with phenylhydrazine because the unsubstituted nitrogen atom in phenylhydrazine,

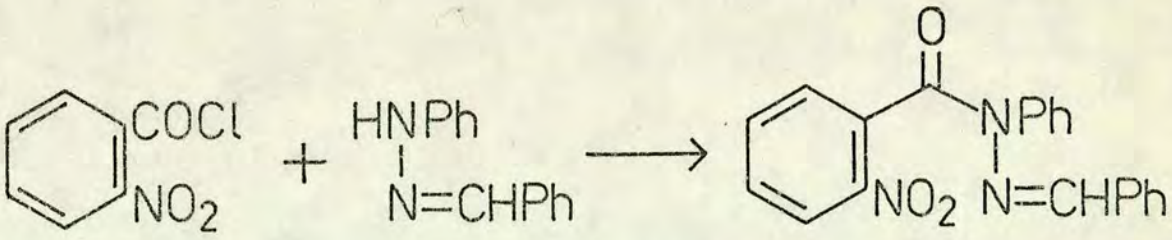


(280)



(281)

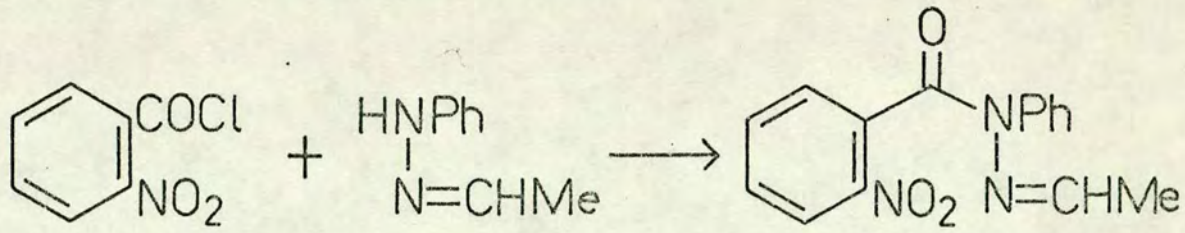
being the more nucleophilic, would condense in preference forming the isomeric product (281). On the other hand, the condensation of 2-nitrobenzoyl chloride with benzylidene-phenylhydrazine proceeded as desired to yield 2-benzylidene-1-(2-nitrophenyl)-1-phenylhydrazine (282)[104].



(282)

However, the attempted hydrolysis of the benzylidene derivative (282) by hydrogen chloride to afford the desired hydrazide (280) as described by Lockemann and Rein[104] failed to remove the protecting group and starting material (282) was recovered in almost quantitative yield. Attempted hydrolysis of (282) using aqueous sulphuric acid likewise gave a quantitative recovery of the starting material. Reaction of (282) with aqueous potassium hydroxide resulted in hydrolysis of the hydrazidic linkage giving ortho-nitrobenzoic acid and benzylidenephenylhydrazine.

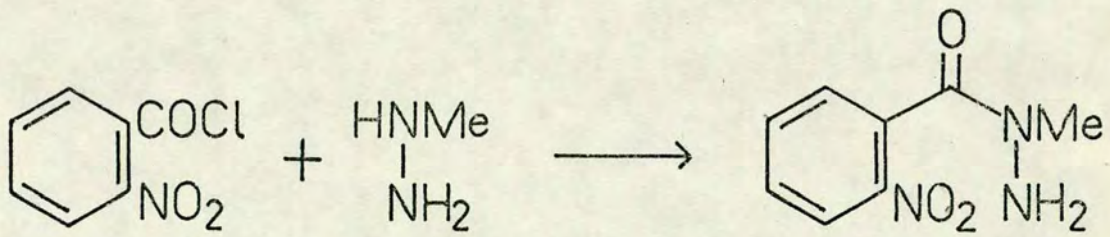
Due to the failure to remove the benzylidene protecting group to afford the desired 2-nitrobenzoylphenylhydrazine (280) it was decided to use an ethylidene protecting group, hoping that its subsequent hydrolysis would proceed more satisfactorily. The condensation of acetaldehyde phenylhydrazone with ortho-nitrobenzoyl chloride in the presence of pyridine gave the desired product (283) in good yield. The i.r. and ^{1}H n.m.r. spectral data and elemental analysis of the product were fully consistent with the assigned structure (283). However, attempted hydrolysis of the



(283)

hydrazide (283) to 2-nitrobenzoylphenylhydrazine (280) using hydrogen chloride produced a multi-component gum.

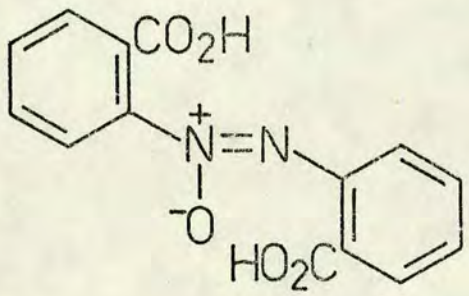
Since the hydrazide (280) proved unobtainable by these synthetic approaches, attention was directed to the synthesis of the methyl analogue (284). In this case direct synthesis is no problem since the presence of the electron-releasing methyl group renders the substituted nitrogen in methyl-



(284)

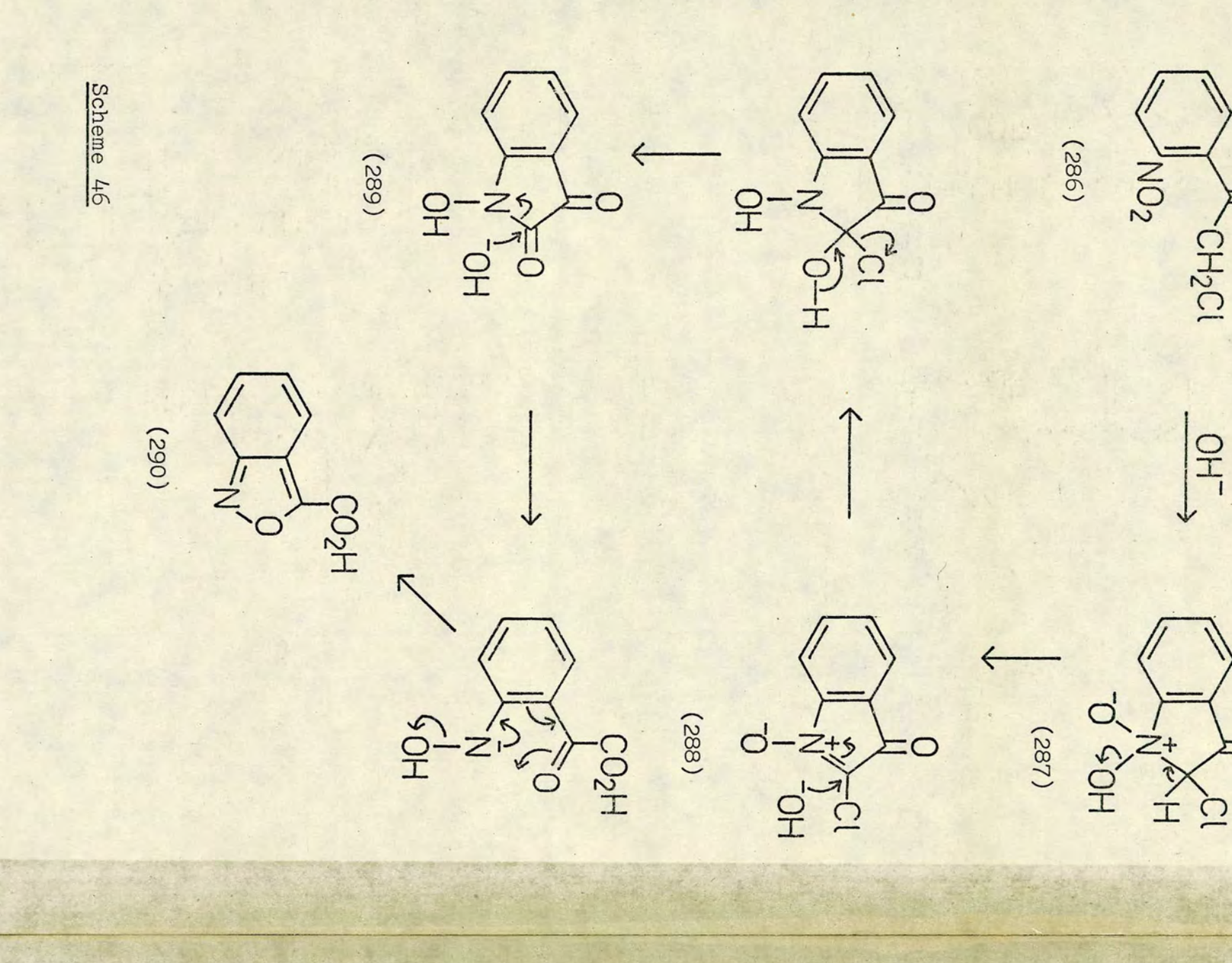
hydrazine the more basic. Thus, the preparation of the hydrazide (284) was readily effected by condensing <u>ortho</u>-nitrobenzoyl chloride in benzene solution with two molar equivalents of methylhydrazine, the hydrogen chloride eliminated forming methylhydrazine hydrochloride. That

condensation produced the desired product was demonstrated by the presence of a single methyl absorption (τ 6.50) in its ^1H n.m.r. spectrum and by bands (3300 and 3200 cm^{-1}) in the i.r. spectrum attributable to a primary amino-group. Reaction of the hydrazide (284) under reflux with aqueous potassium hydroxide gave only a very low recovery of a solid whose i.r. spectrum clearly showed it to be a carboxylic acid. Despite the similar m.p., comparison with an authentic sample (see later), showed that this was not azobenzene-2,2'-dicarboxylic

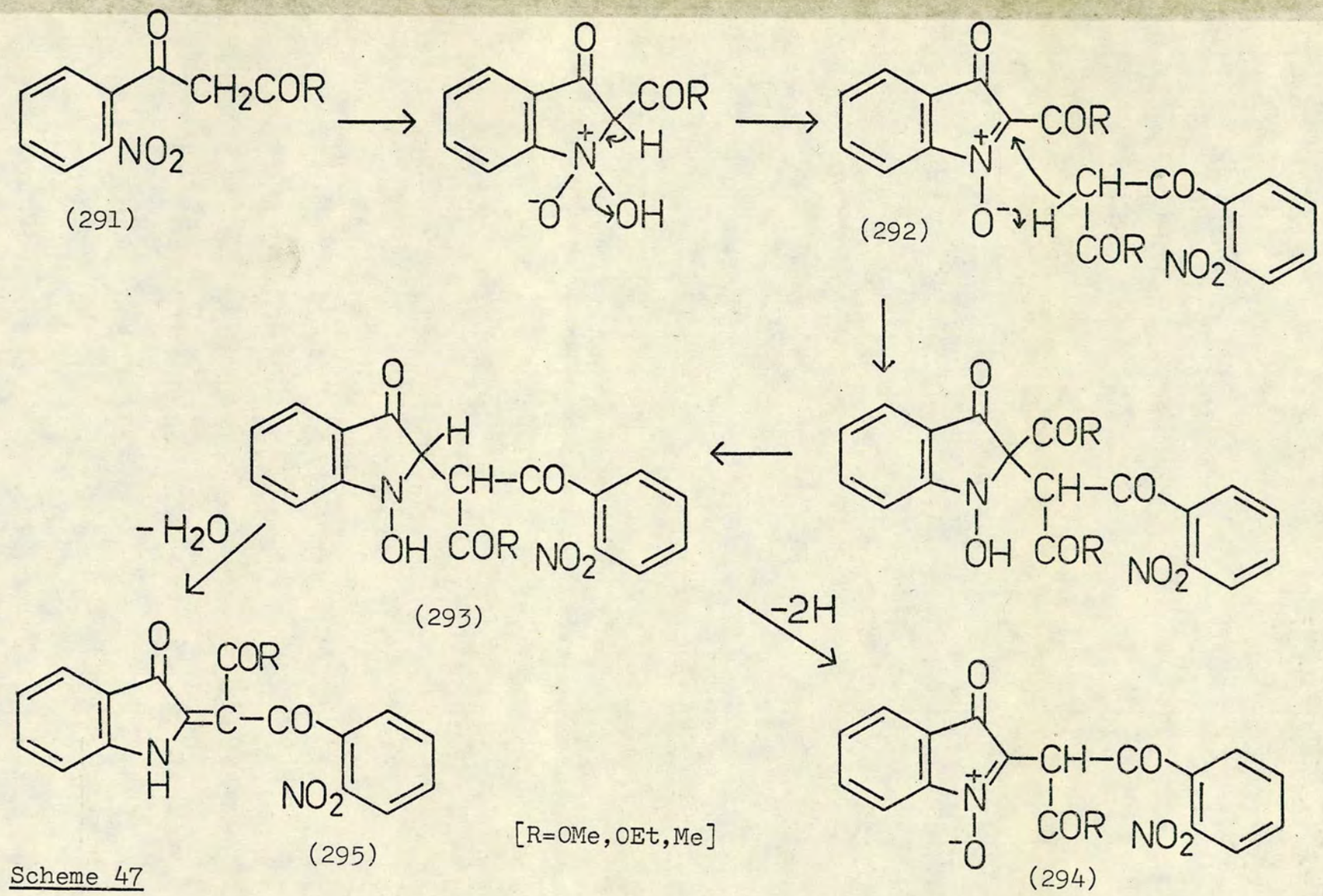


(285)

acid. The m.p. of the unknown acid is also close to that of azoxybenzene-2,2'-dicarboxylic acid (285). However its mass spectrum indicates a weight 17 units less than expected for the azoxyacid (285) though this could be explained by hydrogen abstraction and loss of OH. Unfortunately there was insufficient of the unknown acid for elemental analysis and conclusive proof of structure must await further investigation. The attempted reaction of the hydrazide (284) under milder conditions using aqueous ethanolic sodium carbonate resulted in recovery of the starting hydrazide (284). Finally the attempted reaction of the hydrazide (284) in ethanolic sodium ethoxide gave a low yield of a gum which was shown to be a multi-component mixture and was not further investigated.



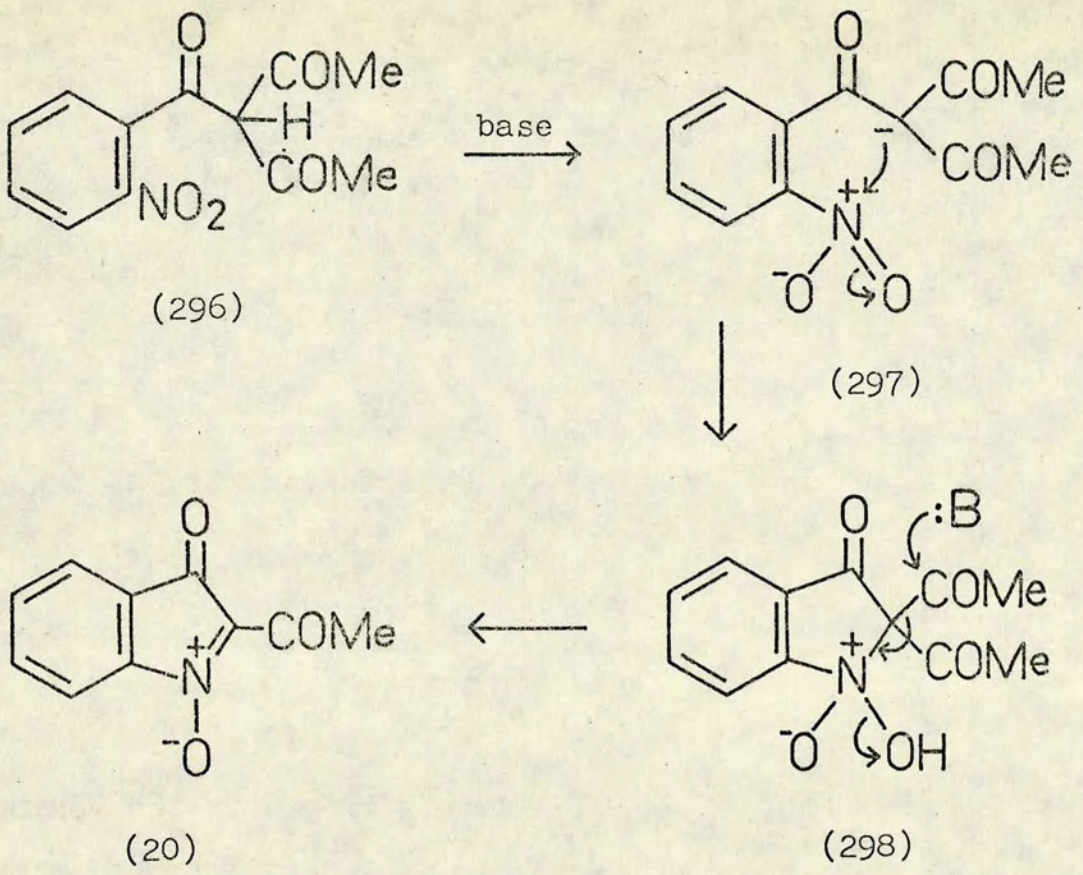
Scheme 46



Scheme 47

2.5 The Base-Catalysed Cyclisation of 2-Nitrobenzoylacetylacetone. A Novel 3-Hydroxyquinoline Synthesis

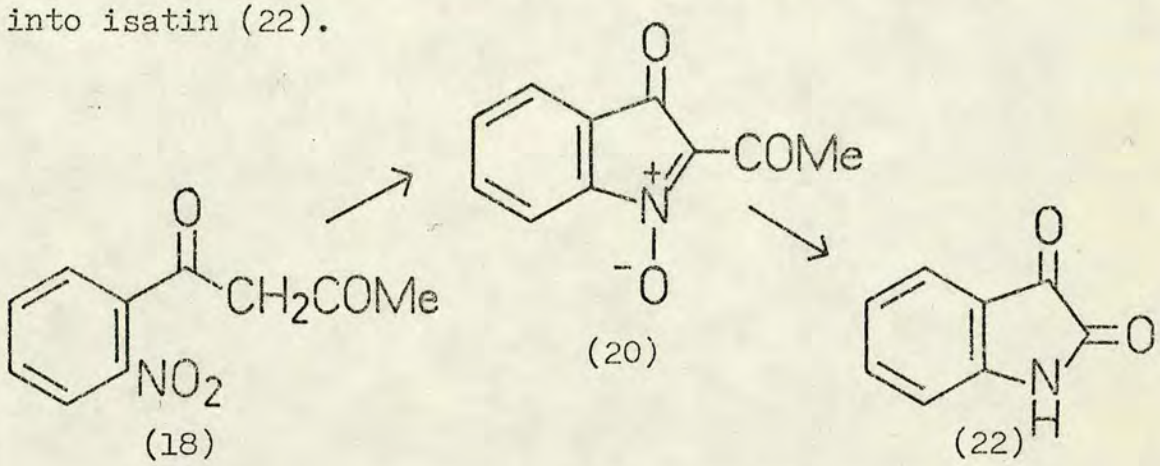
Derivatives of 2-nitroacetophenone, containing an active methylene group, should theoretically be capable of simple aldol-type cyclisations. However, the products of such reactions, the isatogens, are rarely isolated since they are unstable under the basic reaction conditions necessary for their formation. Thus, the transformation of 2-nitrophenacyl chloride (286) in ethanolic alkali into anthranil-3-carboxylic acid (290)[6] is explicable (Scheme 46) in terms of aldol addition to the nitro-group and subsequent dehydration, [(286)→(287)→(288)], to give 2-chloroisatogen (288), which then suffers attack by hydroxide ion, affording 1-hydroxyisatin (289). The known[50] rearrangement of 1-hydroxyisatin (289) to anthranil-3-carboxylic acid (290) lends credence to the final steps, [(288)→ → (290)], of the proposed mechanism (scheme 46). Isatogens (294) have been obtained,[105,106] albeit in low yield, together with indoxyl derivatives (295) from 2-nitrobenzoyl derivatives (291) by the prolonged action (several days) of aqueous sodium hydrogen carbonate. These reactions are readily explained as shown in Scheme 47. The carbanion generated in the side-chain attacks the intact nitro-group to give initially the isatogen (292), which in turn by reaction with a molecule of substrate (291) and subsequent deacylation affords (293). Elimination of water from the adduct (293) yields the indoxyl (295) while oxidation of (293) produces the 2-substituted isatogen (294). The


O
COMe
H
COMe
NO2
base
O
COMe
COMe
N+
O-
O
(296)
(297)
O
:B
COMe
COMe
N+
O-
OH
O
COMe
N+
O-
(298)
(20)

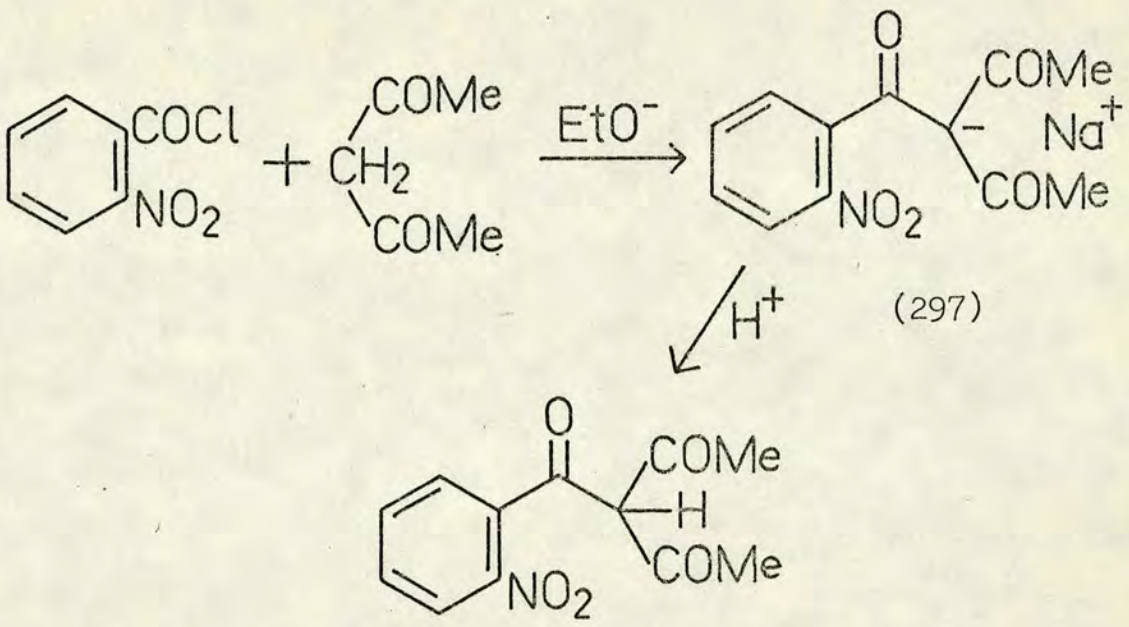
Scheme 48

oxidising agent may well be the initially formed isatogen (292) since isatogens are known[107] to be readily reduced to indoxyls.

It has been noted previously (page 5 and Scheme 6) that 2-acetylisatogen (20) is a plausible intermediate in the conversion of 2-nitrobenzoylacetone (18) in ethanolic alkali into isatin (22).

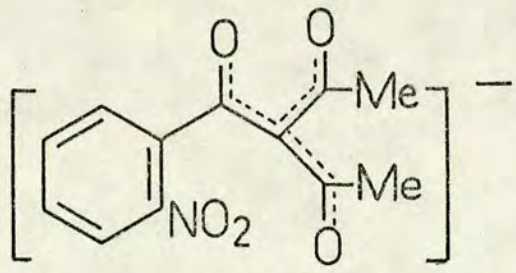


As an extension of the previous work it was decided to study the effect of base on 2-nitrobenzoylacetylacetone (296) in the hope that this tricarbonyl compound (in contrast to the diketone) might give rise to the isatogen (20) as indicated in Scheme 48. The sodium salt (297) of (296), contaminated with some sodium chloride, was prepared[49] by the sodium ethoxide catalysed condensation of 2-nitrobenzoyl chloride with acetylacetone and the free compound (296) was obtained from the salt by acidification. The tricarbonyl compound (296) was also synthesised, but in poorer yield, by an adaptation of the method employed by Reynolds and Hauser[108] for the synthesis of diethyl 2-nitrobenzoylmalonate, namely condensation of 2-nitrobenzoyl chloride with the ethoxy-magnesium derivative of acetylacetone.



(296)

The attempted cyclisation of the tricarbonyl compound (296) under weakly basic conditions (ethanolic sodium carbonate) resulted only in quantitative recovery of the starting material (296). Sodium carbonate is certainly sufficiently basic to remove the very acidic hydrogen in (296) to form the salt (297) ring closure of which would give (298)(Scheme 48). However stabilisation of (298) can only occur by loss of an acetyl group, [(298)→(20)],to form the isatogen (20). It appears therefore that the step [(298)→(20)] requires a stronger base than sodium carbonate and consequently no cyclisation is observed. An alternative explanation for the lack of reactivity in (296) may be reduction in the nucleophilicity of the tertiary carbon due to delocalisation of the negative charge in (297) over the three carbonyl groups as shown in (299). In order to test the hypothesis that cyclisation requires a stronger base,2-nitrobenzoylacetylacetone (296) was heated under reflux with 20% aqueous

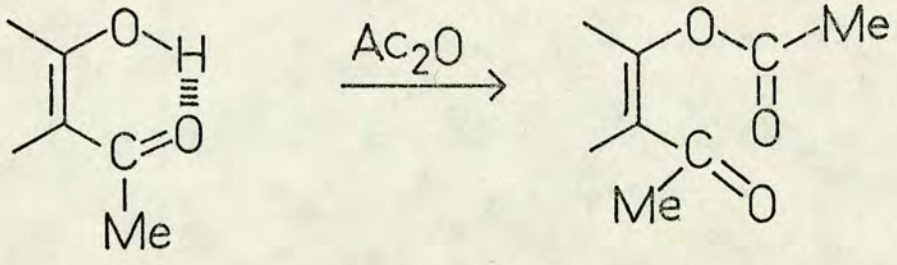


(299)

ethanolic potassium hydroxide. This gave a good yield of a yellow product (A) which was also formed when the sodium salt (297) was subjected to the same reaction conditions. The presence of the contaminating sodium chloride in (297) had no effect on the course of the latter reaction. The product (A) lacked i.r. absorption due to a nitro-group and analysed correctly for $C_{11}H_9NO_2$ which is consistent with the formal loss of carbon dioxide and water from the triketone (296).

The ^1H n.m.r. integral of (A) demonstrated the presence of five low field protons, corresponding to the original four benzenoid protons of the triketone and a fifth deshielded hydrogen. The ^1H n.m.r. spectrum of (A) contained a singlet at τ 7.09 and this together with i.r. absorption at 1650 cm^{-1} indicated the presence of a single acetyl group. Heating (A) with hydrazine hydrate gave a hydrazone whose i.r. spectrum showed no carbonyl absorption and whose elemental and mass spectral analysis established that it was a mono-hydrazone. This confirmed the presence of only one carbonyl group in (A). A sharp singlet at τ -1.16, which disappeared on shaking the sample with D_2O, suggested the presence of a hydroxyl or NH group although the i.r. spectrum of (A) lacked absorption

> 3000 cm^{-1}. Reaction of (A) with acetic anhydride gave a mono-acetoxy derivative (B) which showed i.r. carbonyl absorption at 1750 cm^{-1} favouring its formulation as a C-acetoxy compound rather than an N-acetoxy product which exhibit characteristic[4] i.r. absorption at ca. 1800 cm^{-1}. The formation of a C-acetoxy derivative demonstrates that the hydroxyl group in (A) is bonded to carbon rather than to nitrogen. A further interesting feature of the i.r. spectrum of (B) is the higher frequency of the acetyl carbonyl absorption (1690 cm^{-1}) compared with that (1650 cm^{-1}) in (A). This increase in i.r. carbonyl frequency can be accommodated by the removal (on acetylation) of hydrogen bonding suggesting that in (A) the acetyl and hydroxyl groups are attached to

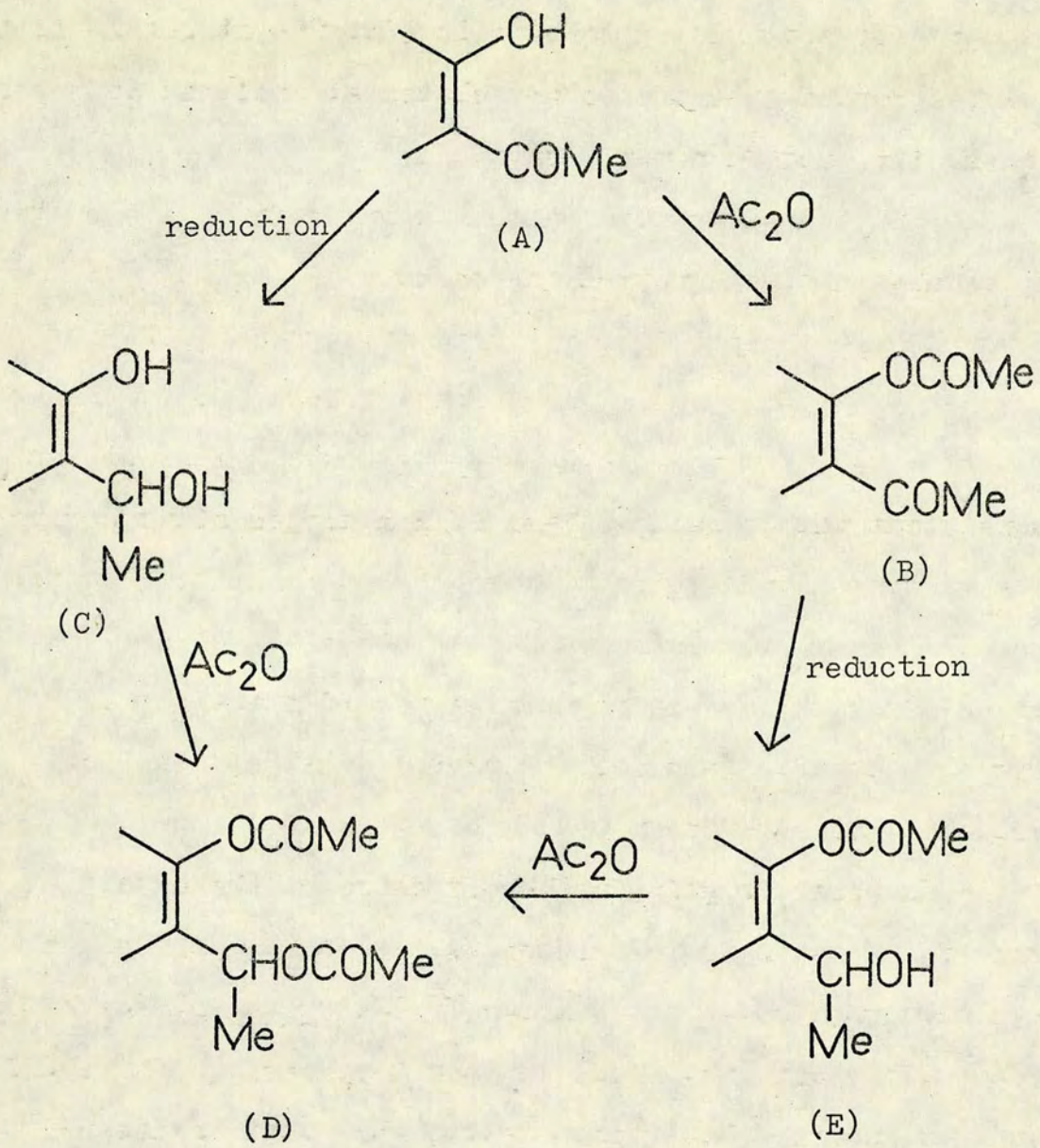


(A) (B)

Scheme 49

adjacent carbon atoms (Scheme 49). Mild hydrolysis of the acetoxy derivative (B) regenerated (A) demonstrating that no rearrangement had occurred during acetylation.

Reduction of (A) by either sodium dithionite or by catalytic hydrogenation afforded (C) whose elemental and mass spectral analysis indicated a gain of two hydrogen atoms during the reduction. Loss of the i.r. carbonyl absorption

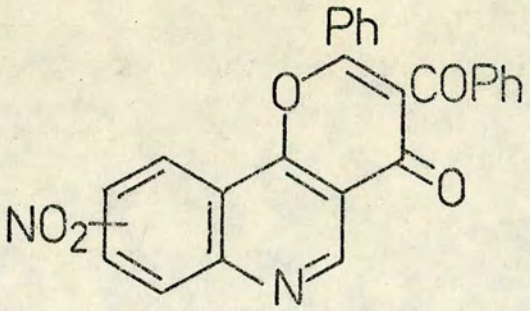

OH
COMe
reduction
(A)
Ac2O
OH
CHOH
Me
(C)
OCOMe
COMe
(B)
Ac2O
reduction
OCOMe
CHOCOMe
Me
(D)
Ac2O
OCOMe
CHOH
Me
(E)

Scheme 50

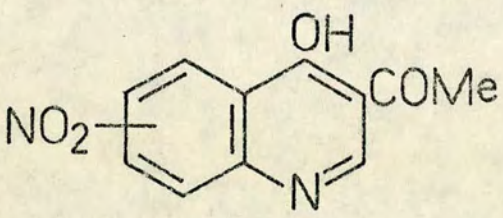
and the reappearance of a band (> 3000 cm^{-1}) due to a hydroxyl function was consistent with reduction of the acetyl group in (A) to an α-hydroxyethyl function, whose presence in (C) was confirmed by the quartet (1H) and the doublet (3H) in the ^1H n.m.r. spectrum. Reaction of (C) with acetic anhydride to yield a diacetoxy derivative (D) (Scheme 50), substantiated the presence of two hydroxyl groups in (C). The structure of (D) was reinforced by satisfactory elemental analysis and spectral (mass, i.r. and ^1H n.m.r.) data.

When (B) was reduced either using sodium dithionite or by catalytic hydrogenation the product (E) had no i.r. absorption corresponding to the acetyl group in (B) but did contain absorption due to a hydroxyl group. That the acetyl function had been reduced to an α-hydroxyethyl group was consistent with a gain in mass of 2 hydrogen atoms during the reduction and was established by the splitting pattern in the ^1H n.m.r. spectrum. Acetylation of the hydroxyl group in (E) afforded an acetoxy derivative identical in all respects to (D), thus completing the cyclical reaction sequence shown in Scheme 50.

In order to gain further evidence on the adjacency of the acetyl and hydroxyl groups in (A) it was decided to attempt pyrone formation. It is known[109] that ortho-hydroxyketones react with acid anhydrides to form 4-pyrones. Thus, Elliot and Tittensor[110] have demonstrated that heating the 6-, 7- or 8-nitro derivatives of 3-acetyl-4-hydroxyquinoline (300) with benzoic anhydride and triethylamine yields a mixture of the pyranoquinolines (301) and (302). This condensation is clearly dependent on the adjacency of the acetyl and hydroxyl



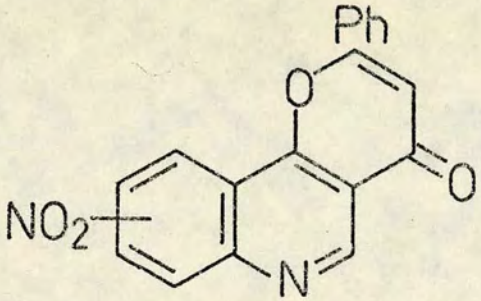
(301)



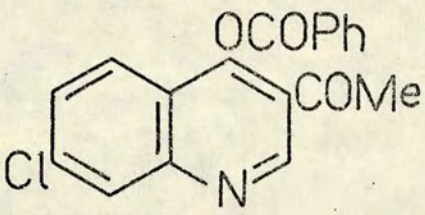
(300)

$(PhCO)_2O$ →

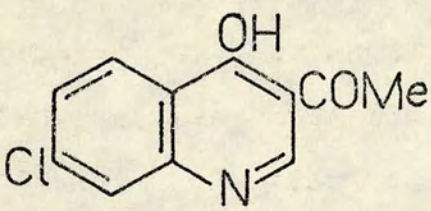
+



(302)



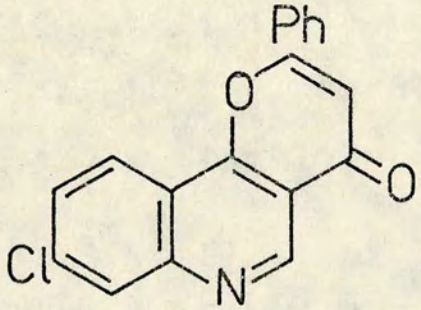
(304)



(303)

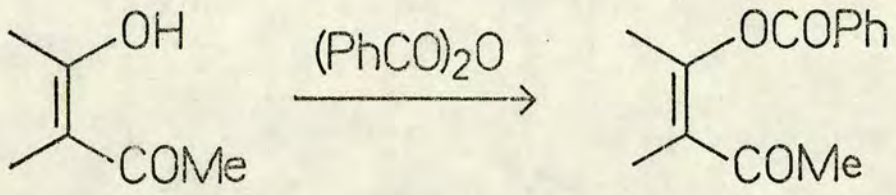
$(PhCO)_2O$ →

+



(305)

functions and the demonstration of a similar reaction with (A) would provide conclusive evidence for the adjacency of the acetyl and hydroxyl groups in (A). When (A) was reacted with benzoic anhydride in the presence of triethylamine the product (identified on the basis of its elemental analysis and its mass and i.r. spectra) was the benzoyloxy derivative (F)

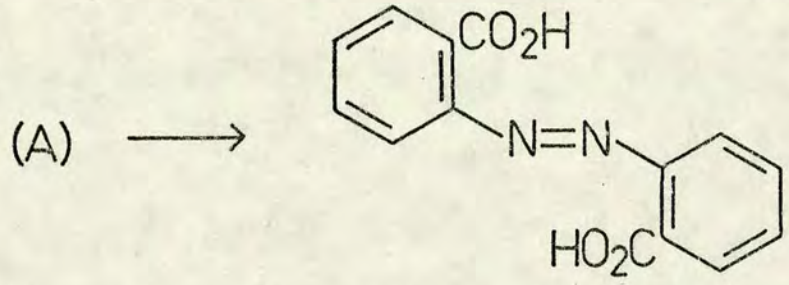


(A) (F)

of (A). However this result does not exclude a structure for (A) in which the hydroxyl and acetyl groups are adjacent since the reaction of the quinoline (303) with benzoic anhydride also yields the benzoyloxy derivative (304) as well as the pyranoquinoline (305).[110]

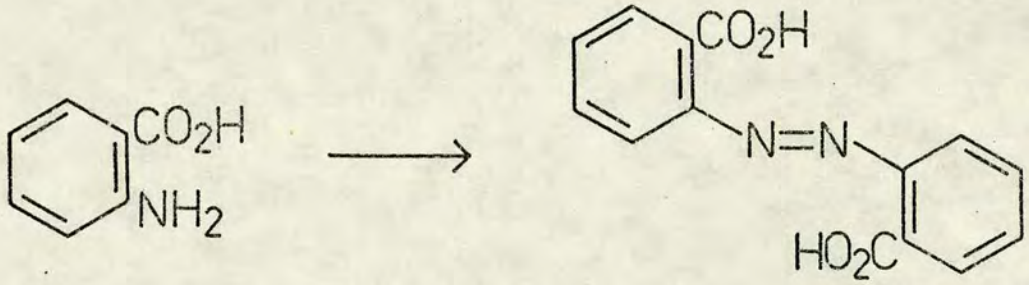
At this stage the nature of the heterocyclic nucleus in (A) was unknown and there was an obvious need to degrade (A) to an identifiable molecule. The attempted alkaline hydrolysis of (A) under forcing conditions (potassium hydroxide in triethylene glycol) either gave the starting material or intractable gums. However oxidative degradation of (A) was more successful. The attempted oxidation of (A) using chromium trioxide or sodium dichromate under a variety of conditions gave intractable inorganic complexes which could not be converted into any recognisable products. On the other

hand, hot alkaline permanganate oxidised (A) in moderate yield to a product identified as azobenzene-2,2'-dicarboxylic acid (306). The isolation of this product is most readily



(306)

explained in terms of the formation and oxidative dimerisation of anthranilic acid. This contention was supported by the

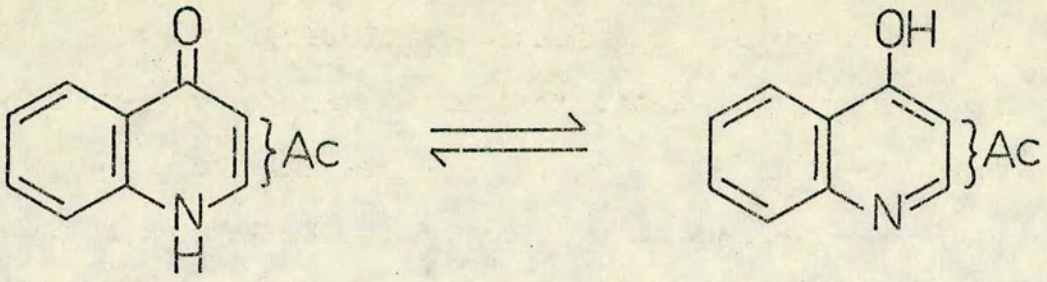


(306)

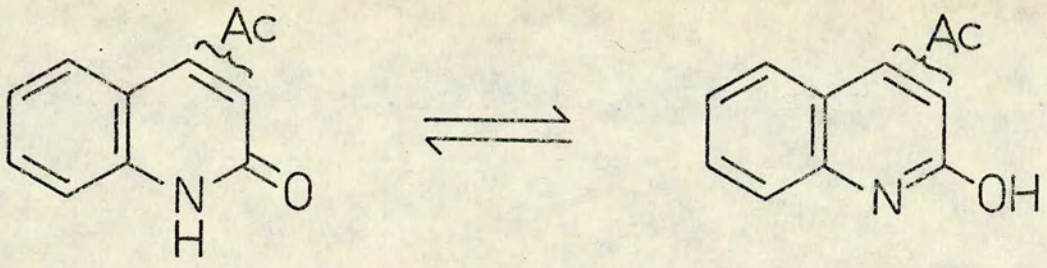
isolation of anthranilic acid when (A) was oxidised with alkaline permanganate at room temperature.

The oxidative formation of anthranilic acid from (A) in conjunction with the other evidence amassed is consistent with the presence of a quinoline nucleus in (A) since alkaline permanganate is known[111] to oxidise 2-substituted quinolines (307) to N-acylanthranilic acids (308), hydrolysis of which would account for the formation of anthranilic acid from (A).

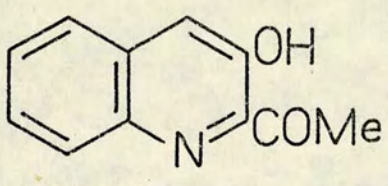
Since the spectroscopic properties of (A) were



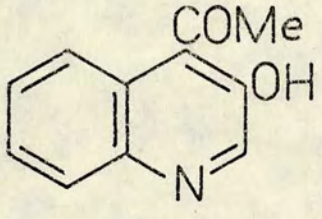
(309)



(310)



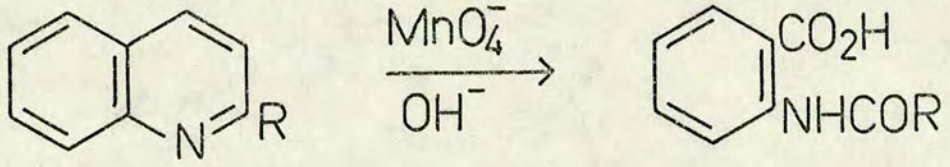
(311)



(312)

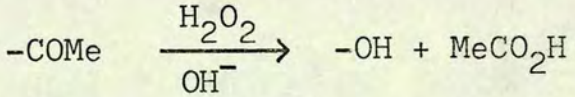
inconsistent with quinolinone structures, (309) and (310), the only other possibility is that (A) is 2- or 4-acetyl-3-hydroxyquinoline, (311) or (312). The presence of a 3-hydroxyquinoline nucleus in (A) was indicated by the u.v. spectrum of the reduction product (C) which exhibited bands at 317 and 330 nm (log ε 3.71 and 3.78) akin to those in 3-hydroxyquinoline which exhibits[112] u.v. absorption at 321 and 330 nm (log ε 3.6).

Support for the formulation of (A) as 2-acetyl-3-hydroxyquinoline was provided by specific oxidation using hydrogen peroxide or peracids.



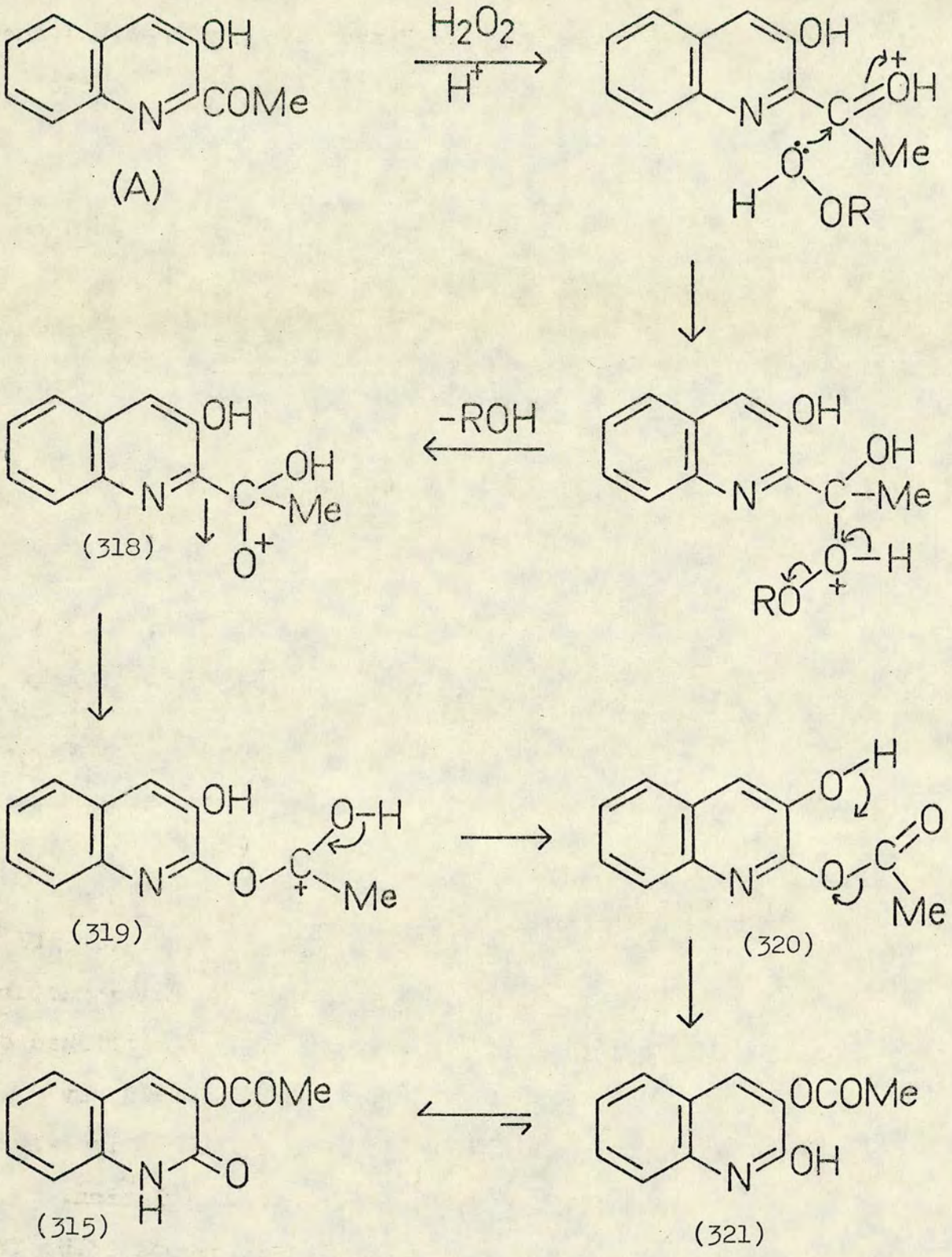
(307) [R=Me,Et,Ph] (308)

Since (A) was known to contain an acetyl group an attempt was made to effect Dakin oxidation [(313)→(314)].



(313) (314)

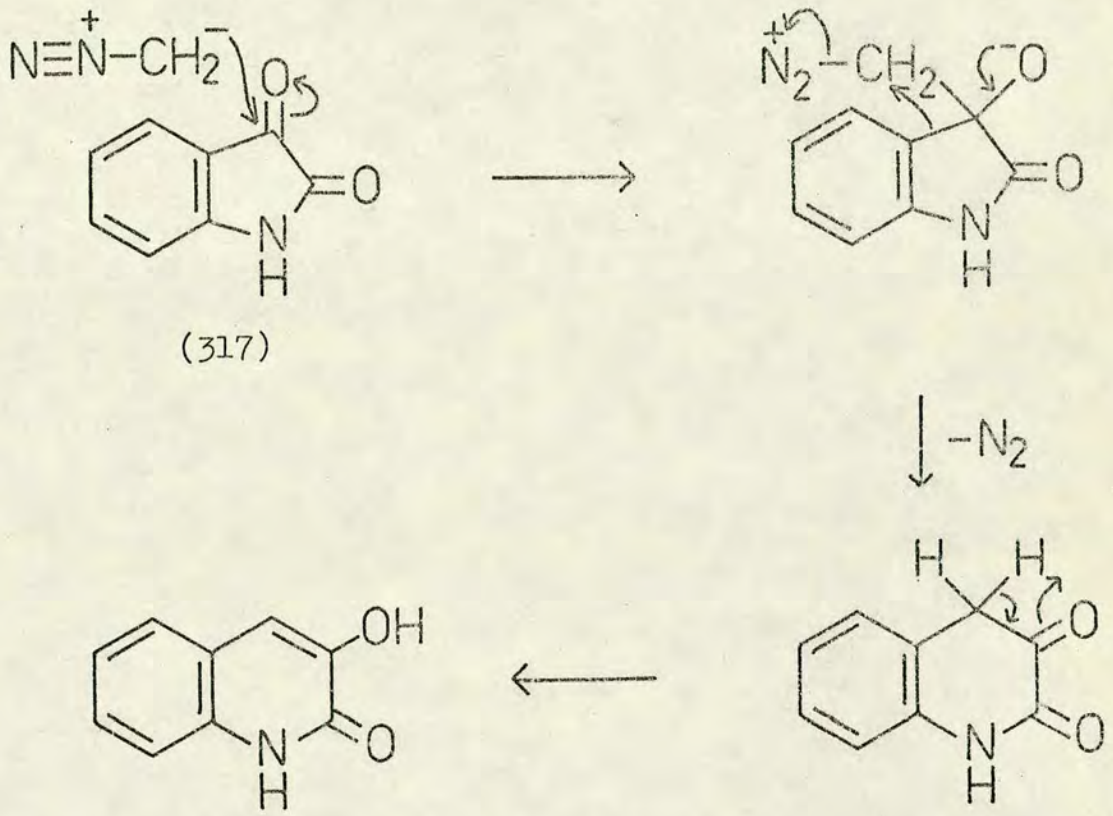
However (A) was unaffected by treatment with alkaline hydrogen peroxide. In contrast the oxidation of (A) using hydrogen peroxide in acetic acid or m-chloroperbenzoic acid gave the same product which showed i.r. absorption typical of a



Scheme 52

[R = MeCO–]

quinolinone and was identified as 3-acetoxyquinolin-2(1H)-one (315) by its ready hydrolysis to 3-hydroxyquinolin-2(1H)-one (316). The latter product was identical to an authentic



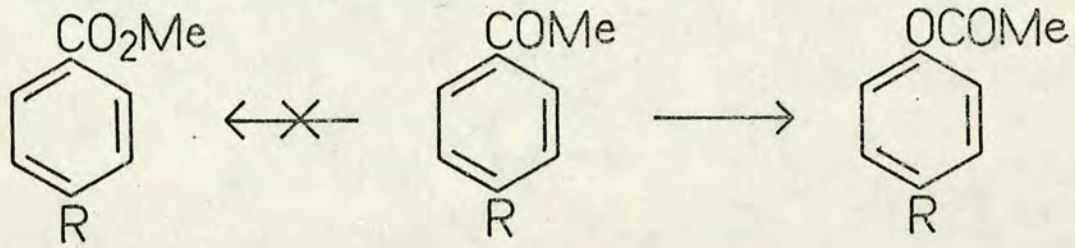
(317) (316)

Scheme 51

sample synthesised[113] by the ring expansion of isatin (317) with diazomethane as indicated in Scheme 51. The structure of 3-acetoxyquinolin-2(1H)-one (315) was further established by its synthesis from 3-hydroxyquinolin-2(1H)-one (316) by acetylation.[114] Only the phenolic hydroxyl group in 3-hydroxyquinolin-2(1H)-one (316) readily underwent acetylation.

The formation of 3-acetoxyquinolin-2(1H)-one (315) from (A) fully substantiates the presence of the quinoline nucleus and is readily rationalised as shown in Scheme 52. In the Baeyer-Villiger oxidation of (A)(Scheme 52) the migration of the heteroaromatic nucleus in preference to methyl [(318)→(319)]

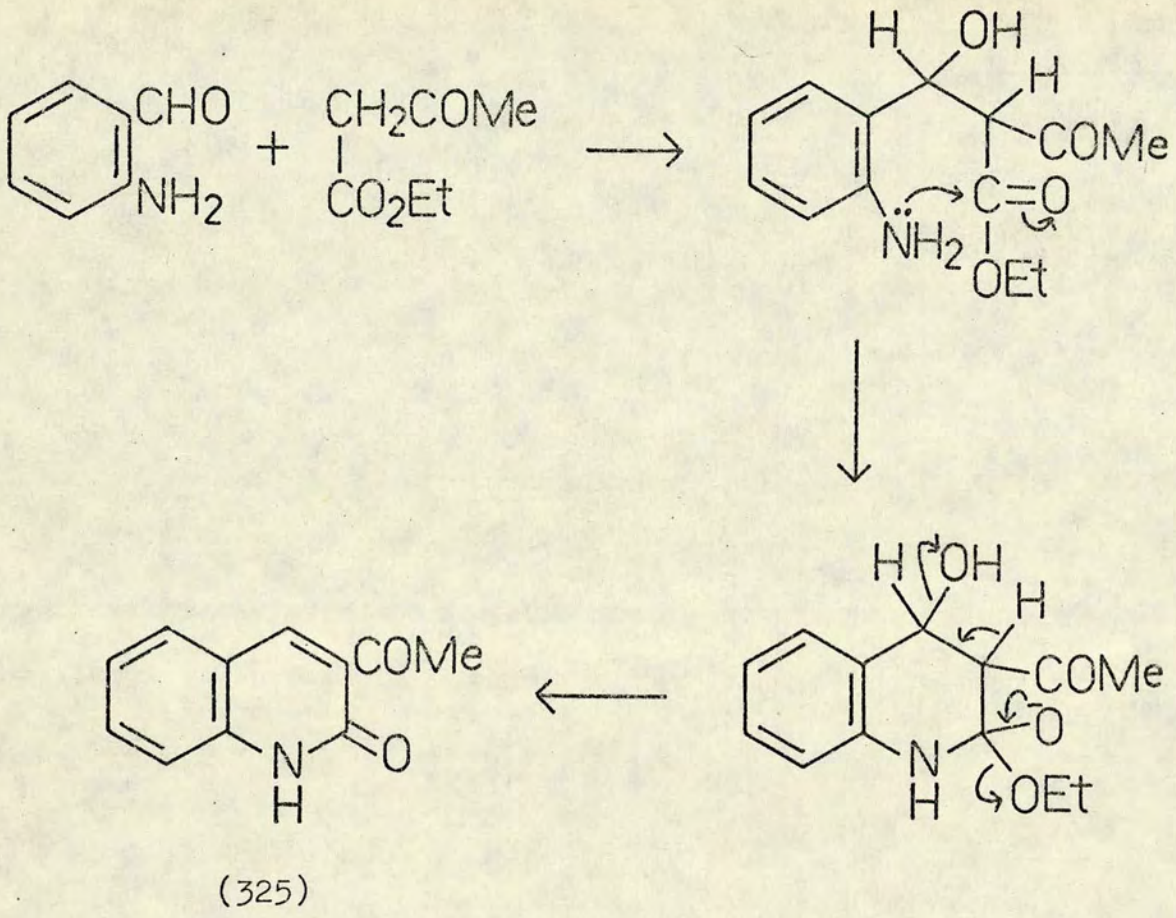
is consistent with the similar migratory preference shown by the Baeyer-Villiger rearrangements of other alkyl-aryl ketones. Thus the acetophenones (322) on peracid oxidation give the phenylacetates (323a)[115,116] and (323b)[117] by



(324) (322) (323)

R
a; H
b; Cl

migration of the phenyl group, rather than the methyl benzoates (324) which would be formed by shift of a methyl group. Subsequent intramolecular acetyl migration [(320)→(321); Scheme 52] then explains the formation of 3-acetoxyquinolin-2(1H)-one (315). The alternate 4-acetyl-3-hydroxyquinoline (312) structure for (A) cannot account for the formation of 3-acetoxyquinolin-2(1H)-one under the conditions of peracid oxidation and can thus be eliminated. The possibility that (A) is in fact 3-acetylquinolin-2(1H)-one (325) and undergoes direct Baeyer-Villiger oxidation to 3-acetoxyquinolin-2(1H)-one (315) can be excluded on two counts. As already shown the spectroscopic properties of (A) are incompatible with a quinolin-2(1H)-one structure. In addition, the chemical properties and transformations of (A) are completely dissimilar to those of 3-acetylquinolin-2(1H)-one (325) which has been synthesised unambiguously by



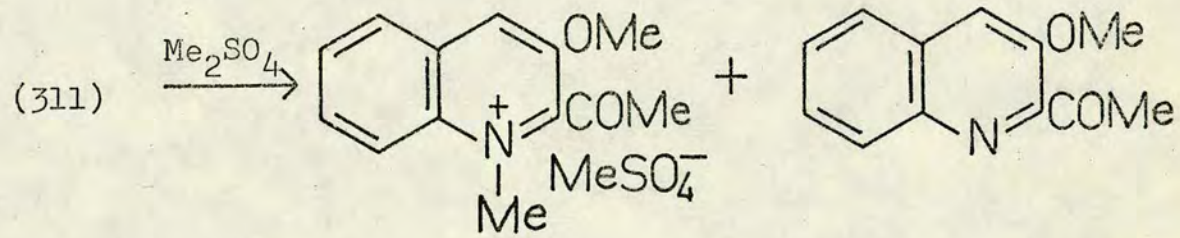
(325)

Scheme 53

(325) (315)

Friedlander and Gohring[118] by condensing ortho-aminobenzaldehyde with ethylacetoacetate as shown in Scheme 53.

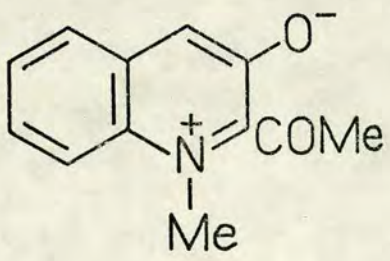
Conclusive evidence that (A) is in fact 2-acetyl-3-hydroxyquinoline (311) was provided by investigations of its behaviour on methylation. Reaction of (A) with dimethyl sulphate in the presence of potassium carbonate under reflux gave two products identified as the quinolinium methosulphate (326) and 2-acetyl-3-methoxyquinoline (327). In a subsequent



(326) (327)

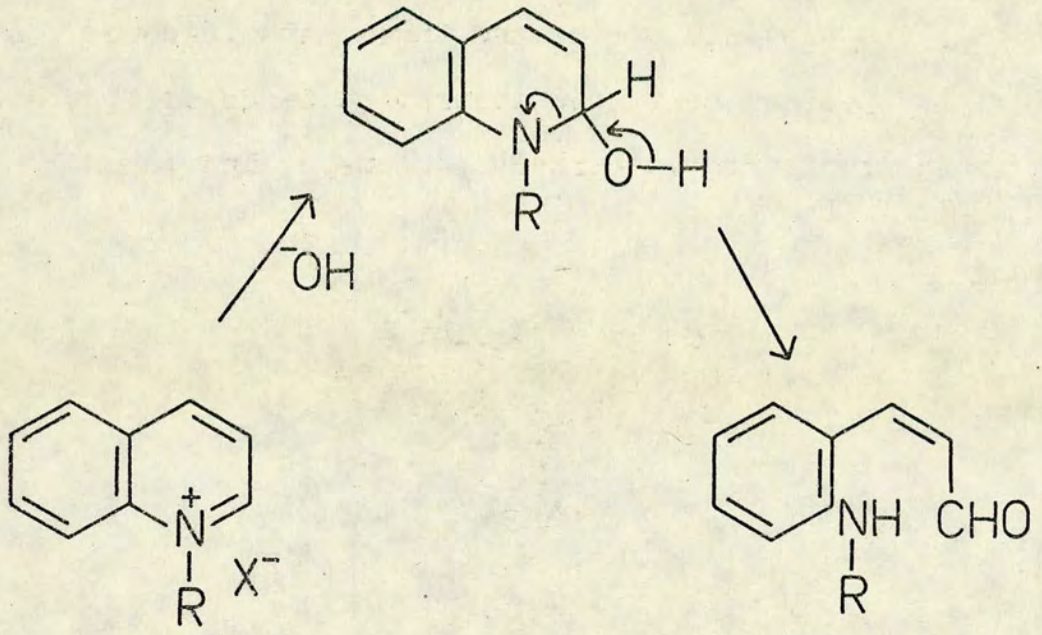
methylation of (A) using dimethyl sulphate in the presence of potassium carbonate but employing a slightly modified work up, the methoxy compound (327) was not isolated. The structures of the compounds (326) and (327) are assigned on the basis of their elemental analysis, spectroscopic properties and in the case of the methosulphate (326) by its chemical properties and transformations. The ready solubility of the

methosulphate in water was in accord with it being a salt and as expected the parent peak in the mass spectrum corresponded to the mass of the cation. Singlet absorptions at τ 5.92 and 6.74 in its ^{1}H n.m.r. spectrum are assigned to the methoxyl and acetyl hydrogens respectively. Of the two lower field signals at τ 5.18 and 5.46 one is due to the methyl group on the quaternary nitrogen, the positive charge inducing deshielding causing these hydrogens to absorb at low field, and the other is due to the hydrogens of the methosulphate ion. The ^{1}H n.m.r. spectrum of the mono-methylated product (327) shows a singlet at τ 7.24 assigned to the acetyl protons and a singlet at τ 6.03. The latter absorption is attributable to the protons of a methoxyl group rather than a quaternary N-methyl group [which by analogy with the ^{1}H n.m.r. absorption of the methosulphate (326) would be expected to absorb at lower field] thus eliminating the otherwise possible betaine structure (328) for the mono-methylated product.

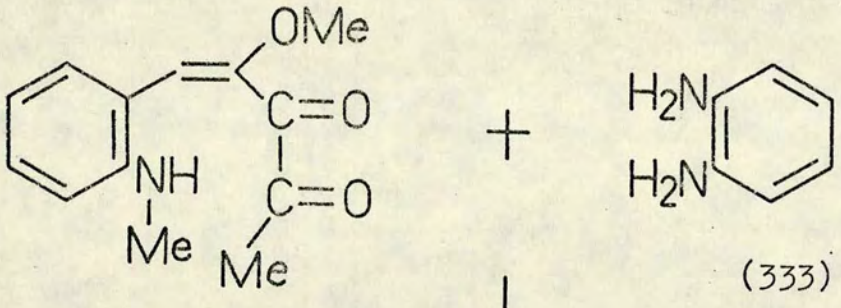


(328)

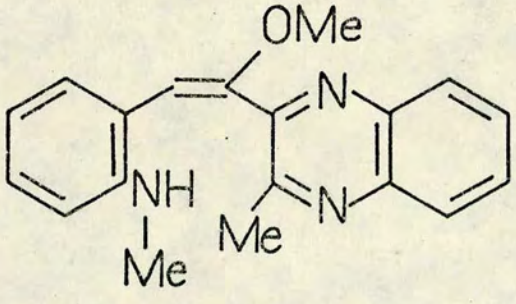
Further support for the structure of the methosulphate (326) was provided by its reaction with cold dilute aqueous sodium hydroxide which gave a very viscous gum whose spectroscopic properties were in accord with the α-diketone structure



(331) (332)

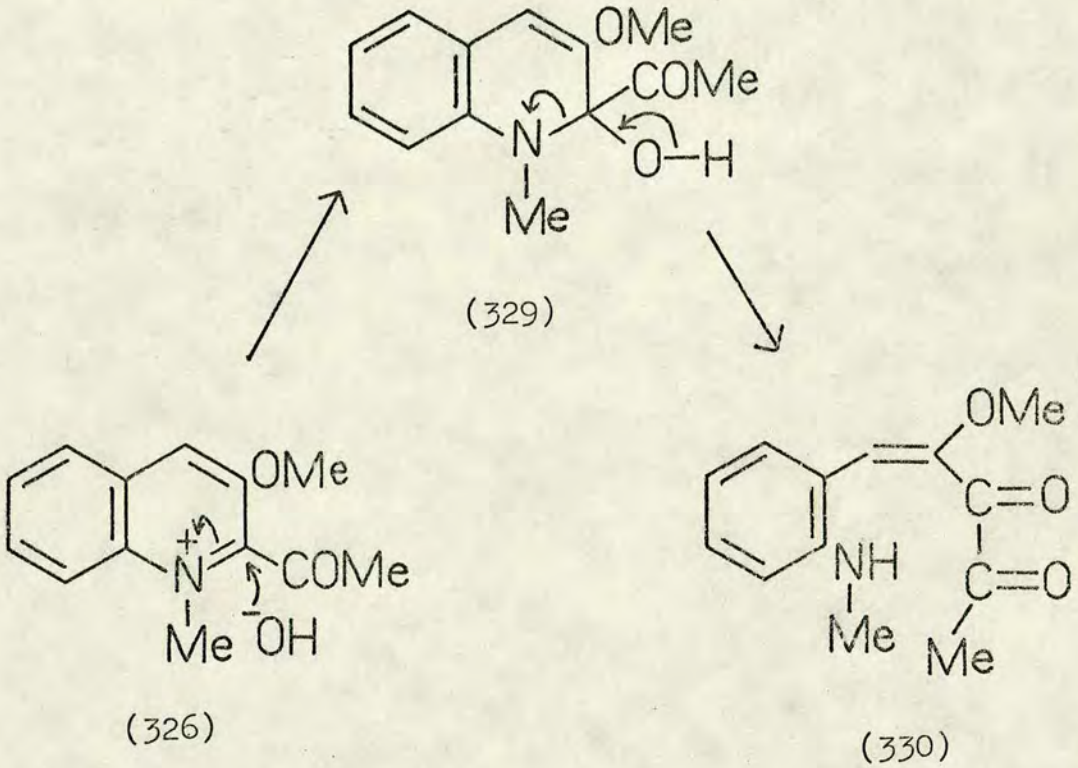


(330) (333)



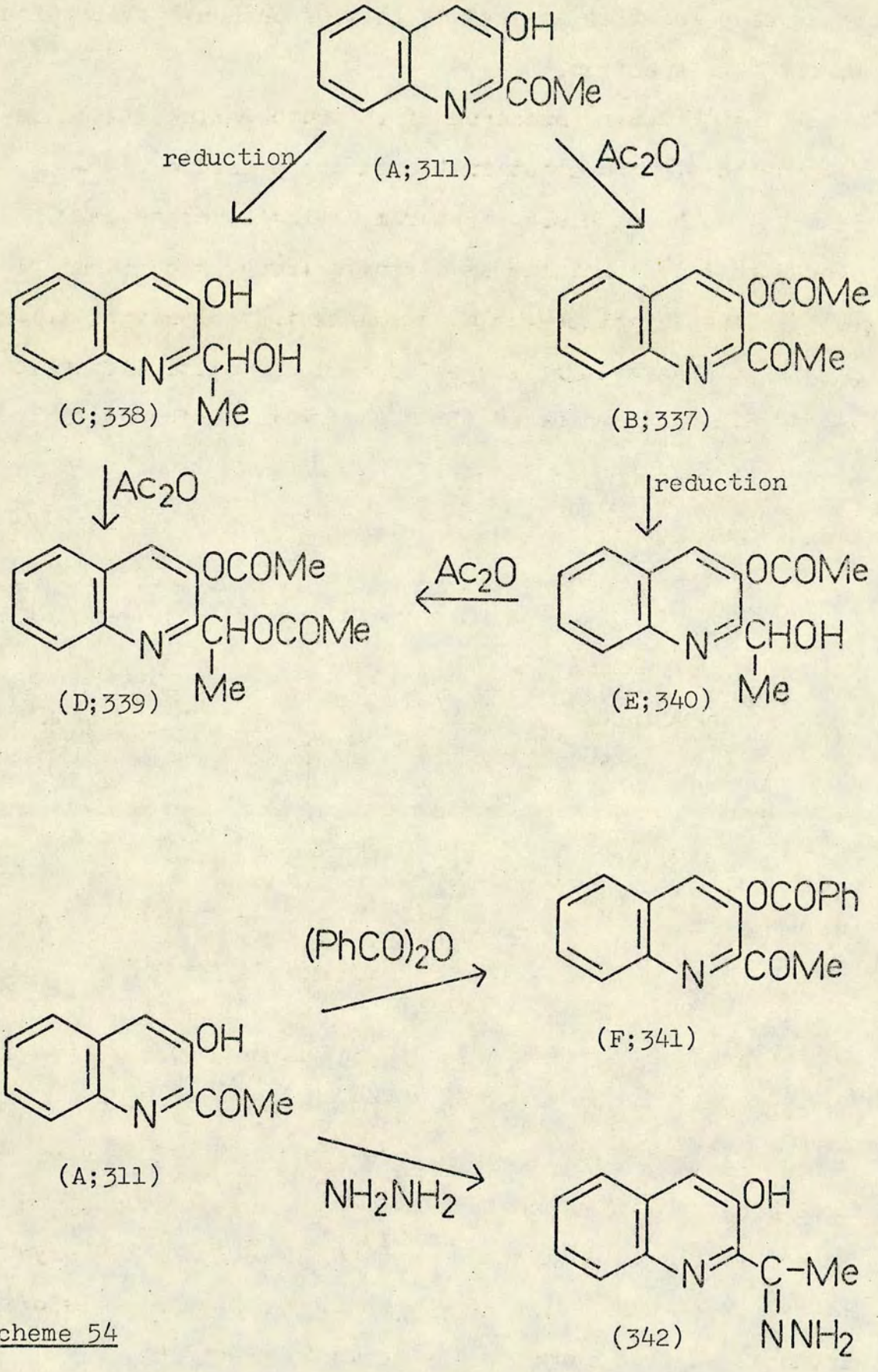
(334)

(330). The ^{1}H n.m.r. spectrum indicated a single amino proton, one olefinic proton and three methyl groups while the i.r. spectrum contained absorption bands attributable to an NH group and two carbonyl groups. The formation of



the diketone (330) is explained by hydroxide ion attack at the 2-position in (326) to form (329), ring opening of which yields (330). This course is entirely analogous to the known[119] ring opening of N-alkyl or N-acylquinolinium halides (331) on reaction with alkali to afford the compounds (332) and so lends weight to the structure of the methosulphate (326).

In further confirmation of the structure (330), reaction of the gum with ortho-phenylenediamine (333) in ethanol afforded the quinoxaline derivative (334). The structure of this product was established by its elemental analysis, mass

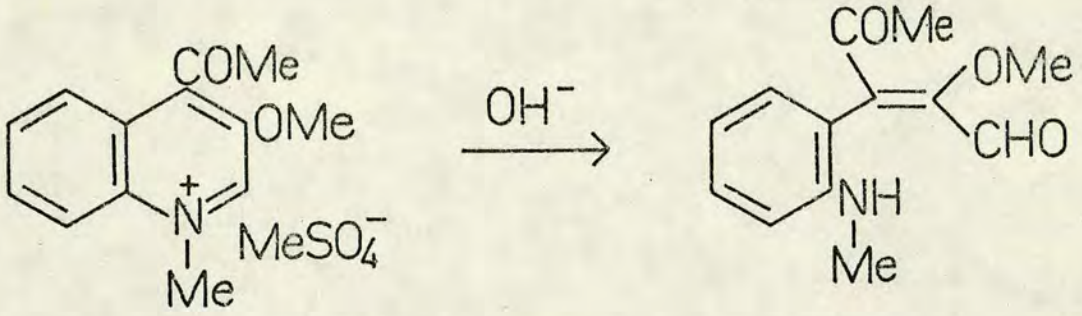

OH
N
COMe
reduction
(A;311)
Ac2O
OH
N
CHOH
Me
(C;338)
OCOMe
N
COMe
(B;337)
Ac2O
reduction
OCOMe
N
CHOCOMe
Me
(D;339)
Ac2O
OCOMe
N
CHOH
Me
(E;340)
(PhCO)2O
OCOPh
N
COMe
(F;341)
OH
N
COMe
(A;311)
NH2NH2
OH
N
C-Me
NNH2
(342)

Scheme 54

spectral properties and by the lack of carbonyl absorption in its i.r. spectrum.

The ^{1}H n.m.r. spectrum of the quinoxaline (334) confirmed the structure but indicated the presence of two isomers. The ^{1}H n.m.r. spectrum of the diketone (330) showed that it consisted of a single isomer and since quinoxaline formation would not cause isomerisation of the olefinic linkage it is suggested that the multiplicity in the ^{1}H n.m.r. spectrum of (334) is due to conformational isomerism as a result of steric crowding.

While it could be argued that the isomeric 4-acetyl-3-hydroxyquinoline (312) would give similar methylation products, reaction of its methosulphate (335) with alkali would afford

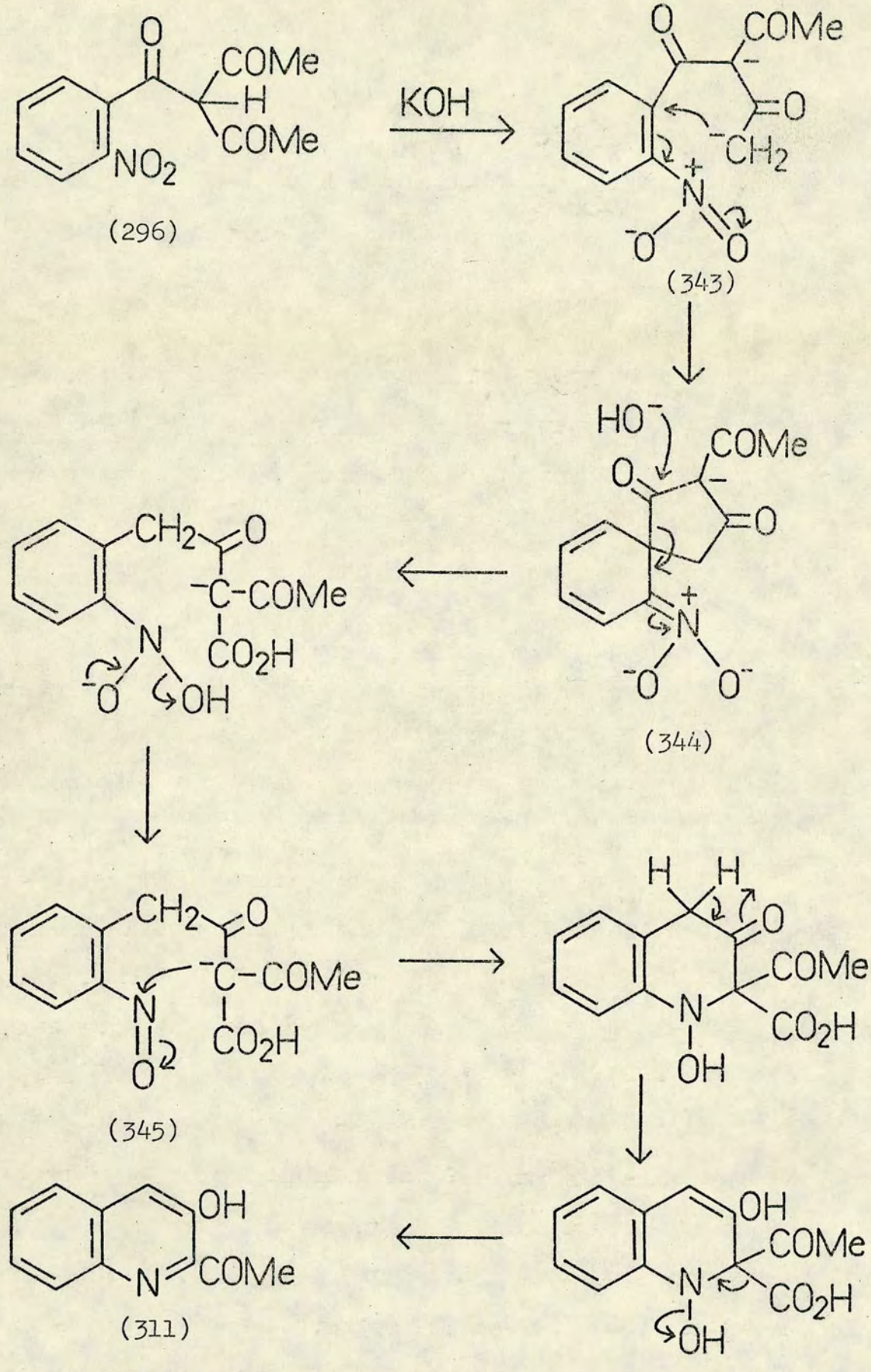


(335) (336)

the aldehyde (336) from which no quinoxaline derivative could be obtained by reaction with ortho-phenylenediamine.

The evidence described before established conclusively that aqueous alkali converts 2-nitrobenzoylacetylacetone (296) into the totally unexpected product, 2-acetyl-3-hydroxyquinoline (311). The full structures of the simple transformation products of this compound are shown in Scheme 54.

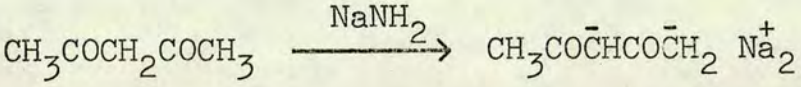
A possible mechanism which accounts for the formation of 2-acetyl-3-hydroxyquinoline (311) from 2-nitrobenzoylacetylacetone is shown in Scheme 55. The production of the



Scheme 55

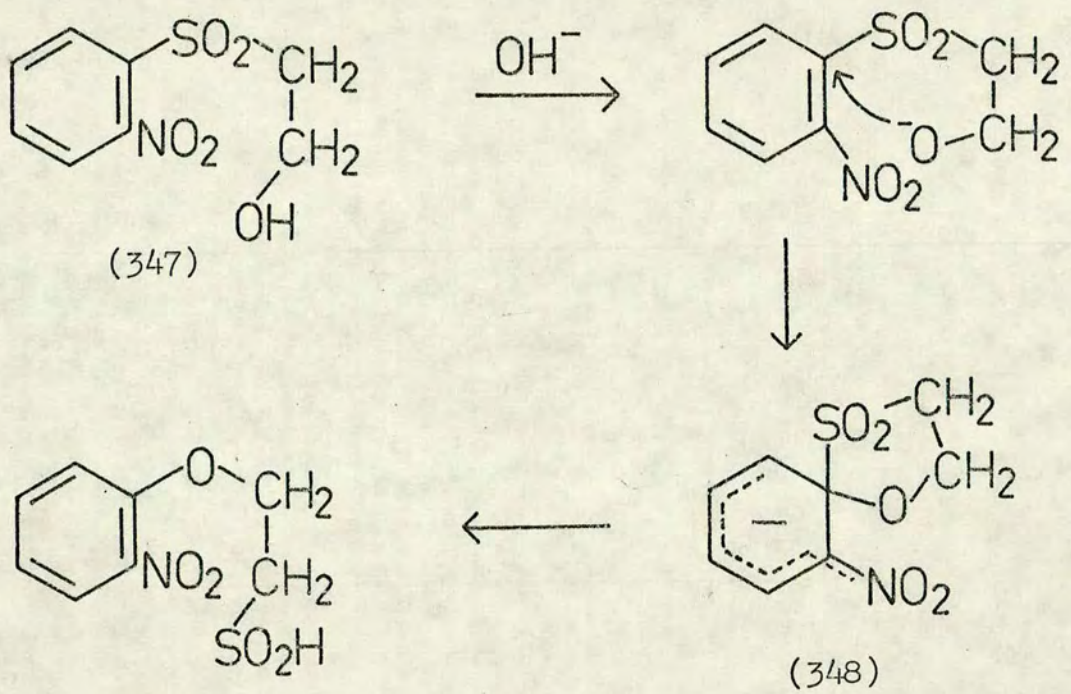
(296) (311)

dianion (343) in the first step is reasonable since acetylacetone likewise forms a dianion (346),[120] albeit on treatment with the stronger base sodamide. The necessity to form



(346)

a dianion explains why the cyclisation to the quinoline is only successful in the presence of a fairly strong base. Nucleophilic attack by the methylene carbanion at the point of attachment of the side-chain to the benzene ring leads to the spiro-intermediate (344). The process [(343)→(344)] is similar to the key step in a group of intramolecular nucleophilic substitution reactions, collectively known as Smiles rearrangements. A representative example[121] is the base-catalysed conversion of the sulphone (347) into the sulphinic acid (349)(Scheme 56). The course of this reaction is governed by the presence of the sulphonyl leaving group, the ejection of which provides the pathway for the conversion of the spiro-intermediate (348) into (349). However in the intermediate (344)(Scheme 55) scission of the benzene-carbonyl bond is energetically unfavourable and the alternative



(347) (348) (349)

Scheme 56

formation of the nitroso-intermediate (345) occurs. Subsequent cyclisation of (345) and aromatisation by decarboxylation then gives 2-acetyl-3-hydroxyquinoline (311) as shown.

Experimental

2.6. Extensions of an N-Hydroxyquinazoline Synthesis

(For general experimental details, see Appendix)

Preparation of Substituted 2-Nitrobenzoic Acids

5-Chloro-2-nitrobenzoic acid was prepared by nitrating[122] 3-chlorobenzoic acid (25%), m.p. 135-8° (from benzene-light petroleum)(lit.,[122] 139°).

Other nitrobenzoic acids were available commercially and were used without further purification.

Preparation of Substituted 2-Nitrobenzoyl Chlorides

5-Chloro-2-nitrobenzoyl chloride (171a)(80%), b.p. 158°/8 mm (lit.,[123] 167°/17 mm) was prepared by reacting 5-chloro-2-nitrobenzoic acid with phosphorus pentachloride.

The following 2-nitrobenzoyl chlorides were prepared by the method described by Taylor and Eckroth.[124]

5-Methyl-2-nitrobenzoyl chloride (171b) (93%) had m.p. 40° (lit.,[125] 46°).

2-Methyl-6-nitrobenzoyl chloride (171c) (90%) had m.p. 39° (lit.,[126] 41°) and was stored at low temperature due to its instability at room temperature.

4-Chloro-2-nitrobenzoyl chloride (171d) (93%) had m.p. 34° (lit.,[127] 34°).

2,6-Dinitrobenzoyl chloride (171e) (95%) had m.p. 96° (lit.,[128] 98°).

2-Nitrobenzoyl chloride was obtained as a pale yellow liquid (95%), b.p. 143°/1 mm (lit.,[124] 141°/0.7 mm).

4-Nitrobenzylaniline (186) was prepared[74] by reacting 4-nitrobenzyl chloride with aniline, (68%), m.p. 68° (from ethanol) (lit.,[129] 72°).

Preparation of N,N-Disubstituted 2-Nitrobenzamides (172a-e)

N-Methylaminoacetonitrile hydrochloride (1.1g, 0.01 mol) was added in one portion to a stirred slurry of fused sodium acetate (3.8g) in glacial acetic acid (23.0ml). A solution of the acid chloride (0.01 mol) in glacial acetic acid (20.0 ml) was then added dropwise with stirring. The reaction mixture was stirred at room temperature for 4h and evaporated under reduced pressure. The residue was treated with water and the solid was collected, washed with water and crystallised to give the pure amides.

N-(5-Chloro-2-nitrobenzoyl)-N-methylaminoacetonitrile (172a) was obtained as colourless plates (92%), m.p. 154° (from ethanol), $\nu_{max.}$ 1660 (CO) and 1540 and 1360 (NO_2) cm^{-1},

	Found:	C,47.3;	H,3.2;	N,16.4%.
$C_{10}H_8ClN_3O_3$ requires:		C,47.3;	H,3.1;	N,16.6%.

N-(5-Methyl-2-nitrobenzoyl)-N-methylaminoacetonitrile (172b) formed colourless crystals (86%), m.p. 88° (from ethanol), $\nu_{max.}$ 1640 (CO), 1530 and 1350 (NO_2) cm^{-1},

	Found:	C,56.5;	H,4.8;	N,18.2%.
$C_{11}H_{11}N_3O_3$ requires:		C,56.7;	H,4.8;	N,18.0%.

N-(4-Chloro-2-nitrobenzoyl)-N-methylaminoacetonitrile (172d) crystallised as colourless needles (85%), m.p. 129° (from ethanol), $\nu_{max.}$ 1650 (CO) and 1540 and 1360 (NO_2) cm^{-1},

	Found:	C,47.7;	H,3.0;	N,16.6%.
$C_{10}H_8ClN_3O_3$ requires:		C,47.3;	H,3.1;	N,16.6%.

N-(2,6-Dinitrobenzoyl)-N-methylaminoacetonitrile (172e) crystallised as colourless plates (80%), m.p. 181° (from

glacial acetic acid-ethanol), $\nu_{max.}$ 1660 (CO), 1550 and 1360 (NO_2) cm^{-1},

Found:	C,45.4;	H,3.1;	N,21.0%.
$C_{10}H_8N_4O_5$ requires:	C,45.4;	H,3.1;	N,21.2%.

N-(2-Methyl-6-nitrobenzoyl)-N-methylaminoacetonitrile (172c)

The attempted condensation of 2-methyl-6-nitrobenzoyl chloride with methylaminoacetonitrile hydrochloride as described before gave only 2-methyl-6-nitrobenzoic acid and an unidentified gum. The amide (172c) was obtained by the following modified procedure.

N-Methylaminoacetonitrile hydrochloride (4.2g, 0.04mol) was treated with saturated aqueous sodium hydrogen carbonate (20.0ml) and chloroform (30.0ml). The chloroform layer was separated, dried and evaporated to give the free amine (1.7g, 61%).

N-Methylaminoacetonitrile (1.4g, 0.02mol) was dissolved in anhydrous benzene (40.0ml), and treated with a solution of 2-methyl-6-nitrobenzoyl chloride (2.0g, 0.01mol) in anhydrous benzene (40.0ml). The mixture was stirred at room temperature for 15h. The insoluble solid was collected, washed with water to remove contaminating amine hydrochloride and combined with a second crop obtained by evaporating the benzene filtrate to give the amide (172c)(total 2.1g, 88%), m.p. 146° (from glacial acetic acid-ethanol), $\nu_{max.}$ 1640 (CO) and 1540 and 1340 (NO_2) cm^{-1},

Found:	C,56.5;	H,4.8;	N,18.2%.
$C_{11}H_{11}N_3O_3$ requires:	C,56.7;	H,4.8;	N,18.0%.

N-2-Nitrobenzoyl-N-4-nitrobenzylaniline (187)

A solution of 2-nitrobenzoyl chloride (2.8g, 0.015 mol) in anhydrous benzene (15.0 ml) was added in one portion to a solution of 4-nitrobenzylaniline (186)(6.8g, 0.03 mol) in anhydrous benzene (100 ml) and the reaction mixture was stirred at room temperature for 48h. The amine hydrochloride was filtered off, the benzene filtrate was evaporated and the residual solid was collected with light petroleum to give the amide (187), which formed yellow-green crystals (5.3g, 94%), m.p. 155° (from glacial acetic acid-ethanol), $\nu_{max.}$ 1650 (CO), 1530 and 1350 (NO_2) cm^{-1},

Found:	C,63.6;	H,4.0;	N,11.2%.
$C_{15}H_{13}N_3O_5$ requires:	C,63.7;	H,4.0;	N,11.1%.

1-Hydroxyquinazolinediones (173a-d)

The corresponding N,N-disubstituted 2-nitrobenzamide (172)(0.01 mol) in absolute ethanol (60.0 ml) was heated under reflux with a solution of sodium (0.9g, 0.04 mol) in absolute ethanol (25.0 ml) for 15 min by which time the initial red colour had faded to orange-yellow. The ethanol was evaporated under reduced pressure and the residue was treated with water and chloroform. The chloroform on work-up gave a negligible amount of gum. The aqueous phase was acidified (dilute aqueous hydrochloric acid), the solid was collected, washed with water and crystallised to afford the pure 1-hydroxyquinazolinediones.

6-Chloro-1-hydroxy-3-methylquinazoline-2(1H),4(3H)-dione (173a) was obtained as colourless needles (86%), sublimes 243° (from

aqueous dimethylformamide), $\nu_{max.}$ 3100br (OH), 1700 and 1600 (CO) cm^{-1}, τ [CF_3COOH] 1.78 [1H,d,J_{meta} 2 Hz, H(5)], 2.14 [1H,dd,J_{ortho} 9 Hz, J_{meta} 2 Hz,H(7)], 2.30 [1H,d,J_{ortho} 9 Hz, H(8)] and 6.34 (3H,s,Me),

Found:	C,47.5;	H,3.1;	N,12.0%.
$C_9H_7ClN_2O_3$ requires:	C,47.7;	H,3.1;	N,12.4%.

3,6-Dimethyl-1-hydroxyquinazoline-2(1H),4(3H)-dione (173b) crystallised as colourless needles (97%), m.p. 224° (subl.) (from glacial acetic acid), $\nu_{max.}$ 3100br (OH), 1700 and 1600 (CO) cm^{-1}, τ [CF_3COOH] 1.98 - 2.44 (3H,m,ArH), 6.36 [3H,s,Me(3)] and 7.52 [3H,s,Me(6)],

Found:	C,58.3;	H,4.8;	N,13.4%.
$C_{10}H_{10}N_2O_3$requires:	C,58.3;	H,4.9;	N,13.6%.

3,5-Dimethyl-1-hydroxyquinazoline-2(1H),4(3H)-dione (173c) formed fine colourless needles (81%), sublimes 233° (from glacial acetic acid), $\nu_{max.}$ 3150br (OH), 1700 and 1660 (CO) cm^{-1}, τ [CF_3COOH] 2.24 - 2.78 (3H,m,ArH), 6.41 [3H,s,Me(3)] and 7.17 [3H,s,Me(5)],

Found:	C,58.3;	H,4.9;	N,13.8%.
$C_{10}H_{10}N_2O_3$ requires:	C,58.3;	H,4.9;	N,13.6%.

7-Chloro-1-hydroxy-3-methylquinazoline-2(1H),4(3H)-dione (173d) was obtained as colourless needles (85%) which tend to turn pink in air, m.p. 265° (subl.)(from glacial acetic acid), $\nu_{max.}$ 3100br (OH), 1710 and 1680 (CO) cm^{-1}, τ [CF_3COOH] 1.84 [1H, d, J_{ortho} 9 Hz, H(5)], 2.25 [1H, d, J_{meta} 2 Hz, H(8)], 2.59 [1H, dd, J_{ortho} 9 Hz, J_{meta} 2 Hz, H(6)] and 6.37 (3H,s,Me),

Found:	C,48.1;	H,3.0;	N,12.5%.
$C_9H_7ClN_2O_3$ requires:	C,47.7;	H,3.1;	N,12.4%.

The Attempted Base-Catalysed Cyclisation of N-(2,6-Dinitrobenzoyl)-N-methylaminoacetonitrile (172e)

(a) The attempted cyclisation of the amide (172e) as described before gave on work up an intractable brown solid (47%) which was not further characterised.

(b) The attempted cyclisation of the amide (172e) as described before but using aqueous sodium carbonate, aqueous sodium acetate or piperidine in ethanol as catalyst gave unchanged starting material (60-79%).

The Reaction of N-2-Nitrobenzoyl-N-4-nitrobenzylaniline (187) with Ethanolic Sodium Ethoxide

(a) The amide (187) (0.8g, 0.002 mol) in absolute ethanol (25.0 ml) was heated under reflux with a solution of sodium (0.2g, 0.008 mol) in absolute ethanol (7.0 ml) for 15 min by which time the original red colour had darkened. The ethanol was evaporated under reduced pressure and the residue was treated with water and chloroform. The chloroform phase on work-up gave a very little red gum which was not investigated. The aqueous alkaline phase was acidified dropwise with dilute aqueous hydrochloric acid to give a light brown solid which was collected and crystallised (from benzene) to yield 2-phenylindazolone (0.07g), m.p. 205°, identified by comparison (m.p. and i.r. spectrum) with an authentic sample.[72] The acidic aqueous filtrate was extracted with chloroform to give 4-nitrobenzoic acid (0.07g), m.p. 238° (from water) identified by comparison (m.p. and i.r. spectrum) with an authentic sample.

(b) The amide (187) (1.9g, 0.005 mol) dissolved in absolute ethanol (160 ml) was treated with a solution of sodium (0.5g, 0.02 mol) in absolute ethanol (20.0 ml). The mixture was stirred at room temperature for 4h and the insoluble solid was collected to give the starting amide (187) (0.7g), identical (m.p. and i.r. spectrum) with an authentic sample. The ethanol was evaporated from the filtrate under reduced pressure and the residue was treated with water and chloroform. The chloroform phase gave a red gum (0.2g) whose t.l.c. in benzene over silica indicated a multi-component mixture. The aqueous alkaline phase gave, on careful acidification to pH 8 with dilute aqueous hydrochloric acid, a light brown solid (0.3g) whose i.r. spectrum (having no sharp absorptions) suggested a complex mixture. The filtrate was acidified and the solid was collected and crystallised to give 4-nitrobenzoic acid (0.2g), m.p. 237° identified by comparison (m.p. and i.r. spectrum) with an authentic sample. A second crop (0.04g) of 4-nitrobenzoic acid was obtained from the chloroform extract of the acidic aqueous filtrate.

1-Acetoxyquinazolinediones (174a-d)

The 1-hydroxyquinazolinediones (173a-d) (0.002 mol) were heated on a boiling water bath for 20 min with acetic anhydride (1.0 ml). The mixtures were allowed to cool and were left at room temperature for a further 20 min. The excess of acetic anhydride was evaporated under reduced pressure and the residues were triturated with ether to afford the acetoxy derivatives (174) which were collected and crystallised.

1-Acetoxy-6-chloro-3-methylquinazoline-2(1H),4(3H)-dione (174a) formed colourless crystals (93%), m.p. 170° (from glacial acetic acid-ethanol), $\nu_{max.}$ 1800, 1720, and 1680 (CO) cm^{-1}, τ [CF_3COOH] 1.74 [1H, d, J_{meta} 2 Hz, H(5)], 2.20 [1H, dd, J_{ortho} 9 Hz, J_{meta} 2 Hz, H(7)], 2.78 [1H, d, J_{ortho} 9 Hz, H(8)], 6.36 [3H, s, Me(3)] and 7.44 [3H, s, Me(1)],

Found:	C,49.0;	H,3.4;	N,10.6%.
$C_{11}H_9ClN_2O_4$ requires:	C,49.2;	H,3.4;	N,10.4%.

1-Acetoxy-3,6-dimethylquinazoline-2(1H),4(3H)-dione (174b) was obtained as colourless crystals (80%), m.p. 126° (from ethanol), $\nu_{max.}$ 1800, 1710 and 1660 (CO) cm^{-1}, τ [CF_3COOH] 1.94 [1H, d, J_{meta} 2 Hz, H(5)], 2.34 [1H, dd, J_{ortho} 9 Hz, J_{meta} 2 Hz, H(7)], 2.90 [1H, d, J_{ortho} 9 Hz, H(8)], 6.17 [3H,s,Me(3)], 7.47 [3H,s,Me(1) or Me(6)] and 7.53 [3H,s,Me (6) or Me(1)],

Found:	C,57.9;	H,4.8;	N,11.8%.
$C_{12}H_{12}N_2O_4$ requires:	C,58.1;	H,4.9;	N,11.3%.

1-Acetoxy-3,5-dimethylquinazoline-2(1H),4(3H)-dione (174c) formed colourless crystals (83%), m.p. 126° (from glacial acetic acid-ethanol), $\nu_{max.}$ 1800, 1710 and 1670 (CO) cm^{-1}, τ [CF_3COOH] 2.35 [1H, t, J_{ortho} 9 Hz, H(7)], 2.74 [1H, dd, J_{ortho} 9 Hz, J_{meta} 2 Hz, H(6)], 2.93 [1H, dd, J_{ortho} 9 Hz, J_{meta} 2 Hz, H(8)], 6.42 [3H,s,Me(3)], 7.15 [3H,s,Me(5)] and 7.46 [3H,s,Me(1)],

Found:	C,58.0;	H,4.9;	N,11.5%.
$C_{12}H_{12}N_2O_4$ requires:	C,58.0;	H,4.8;	N,11.3%.

1-Acetoxy-7-chloro-3-methylquinazoline-2(1H),4(3H)-dione (174d)

formed colourless crystals (98%), m.p. 181° (from glacial acetic acid-ethanol), $\nu_{max.}$ 1800, 1720 and 1680 (CO) cm^{-1}, τ [CF_3COOH] 1.78 [1H, d, J_{ortho} 9 Hz, H(5)], 2.58 [1H, dd, J_{ortho} 9 Hz, J_{meta} 2 Hz, H(6)], 2.75 [1H, d, J_{meta} 2 Hz, H(8)], 6.39 [3H,s,Me(3)] and 7.45 [3H,s,Me(1)],

Found:	C,49.4;	H,3.3;	N,10.8%.
$C_{11}H_9ClN_2O_4$ requires:	C,49.2;	H,3.4;	N,10.4%.

Quinazolinediones (175a-e)

(a) Sodium Dithionite Reduction of 1-Hydroxyquinazolinediones (173a-d)

The 1-hydroxy compounds (173a-d) (0.002 mol) in 70% w/v aqueous ethanol (30.0 ml) were heated under reflux with an equal weight of sodium dithionite for 1h. A second portion of sodium dithionite was added and heating was continued for a further 1h. The mixture was evaporated under reduced pressure, the residue was treated with water (20.0 ml) and the crude product was collected, dried, and crystallised to give the corresponding quinazolinedione (90-96%).

(b) Catalytic Hydrogenolysis of 1-Acetoxyquinazolinediones (174a-d)

The 1-acetoxyquinazolinediones (174a-d) (0.001 mol) in ethanol (100 ml) were hydrogenated at room temperature and atmospheric pressure over 10% palladium-on-charcoal (0.02g). Filtration and evaporation of the ethanol under reduced pressure afforded the crude quinazolinediones (175) (70-90%) which were purified by crystallisation.

3,6-Dimethylquinazoline-2(1H),4(3H)-dione (175b) crystallised as colourless needles, m.p. 265° (subl.)(from ethanol), $\nu_{max.}$ 3300br (OH), 1710 and 1660 (CO) cm^{-1}, τ [CF_3COOH] 2.01 [1H, d, J_{meta} 2 Hz, H(5)], 2.36 [1H, dd, J_{ortho} 9 Hz, J_{meta} 2 Hz, H(7)], 2.81 [1H, d, J_{ortho} 9 Hz, H(8)], 6.40 [3H,s, Me(3)] and 7.54 [3H,s,Me(6)],

Found: C, 63.1; H, 5.2; N, 14.5%.

$C_{10}H_{10}N_2O_2$ requires: C, 63.2; H, 5.3; N, 14.7%.

3,5-Dimethylquinazoline-2(1H),4(3H)-dione (175c) formed colourless rhombic crystals, m.p. 267° (subl.)(from glacial acetic acid-ethanol), $\nu_{max.}$ 3200br (OH), 1700 and 1660 (CO) cm^{-1}, τ [CF_3COOH] 2.39 [1H, t, J_{ortho} 9 Hz, H(7)], 2.79 [1H, d, J_{ortho} 9 Hz, H(5) or H(8)], 2.90 [1H, d, J_{ortho} 9 Hz, H(8) or H(5)], 6.44 [3H,s,Me(3)] and 7.17 [3H,s,Me(5)],

Found: C, 63.2; H, 5.3; N, 14.9%.

$C_{10}H_{10}N_2O_2$ requires: C, 63.2; H, 5.3; N, 14.7%.

7-Chloro-3-methylquinazoline-2(1H),4(3H)-dione (175d) formed colourless crystals, m.p. 268° (subl.)(from glacial acetic acid-ethanol), $\nu_{max.}$ 3300 (OH), 1750 and 1650 (CO) cm^{-1}, τ [CF_3COOH] 1.82 [1H, dd, J_{ortho} 9 Hz, J_{meta} 2 Hz, H(5)], 2.64 [2H,m,H(6) and H(8)] and 6.20 [3H,s,Me(3)],

Found: C,51.6; H,3.3; N,13.4%; M^+212/210.

$C_9H_7ClN_2O_2$ requires: C,51.3; H,3.3; N,13.3%; M 212/210.

Reduction of 6-Chloro-1-hydroxy-3-methylquinazoline-2(1H),4(3H)-dione (173a) by method (a) gave as expected 6-chloro-3-methylquinazoline-2(1H),4(3H)-dione (175a) as colourless

crystals m.p. 162° (subl.) (from glacial acetic acid-ethanol), $\nu_{max.}$ 3100br (OH), 1720 and 1660 (CO) cm^{-1}, τ [CF_3COOH] 1.83 [1H, d, J_{meta} 2 Hz, H(5)], 2.15 [1H, dd, J_{ortho} 9 Hz, J_{meta} 2 Hz, H(7)], 2.72 [1H, d, J_{ortho} 9 Hz, H(8)] and 6.38 [3H, s, Me(3)],

Found:	C,51.5;	H,3.4;	N,13.4%.
$C_9H_7ClN_2O_2$ requires:	C,51.3;	H,3.3;	N,13.3%.

Reduction of 1-Acetoxy-6-chloro-3-methylquinazoline-2(1H), 4(3H)-dione (174a) by method (b) however gave colourless needles of 3-methylquinazoline-2(1H),4(3H)-dione (175e) (90%), m.p. 235° (from glacial acetic acid-ethanol), identical (m.p. and i.r. spectrum) with an authentic sample.[72]

2.7. Studies of Intramolecular Nucleophilic Aromatic Substitution Reactions Leading to Phthalimidines

Preparation of Substituted Benzoic Acids

2-Chloro-3,5-dinitrobenzoic acid was prepared[94] by nitrating 2-chlorobenzoic acid (88%), m.p. 192-6° (lit.,[94] 198°).

3,5-Dinitro-2-methoxybenzoic acid was prepared[130] by nitrating 2-methoxybenzoic acid (64%), m.p. 162-5° (lit.,[130] 166°).

Other nitrobenzoic acids were available commercially and were used without further purification.

Preparation of Substituted Benzoyl Chlorides

2-Nitrobenzoyl chloride was prepared as described before (see page 91).

3-Nitrobenzoyl chloride (251) was prepared[131] by the action of thionyl chloride on 3-nitrobenzoic acid (90%), m.p. 32-4° (lit.,[131] 35°).

2-Chloro-5-nitrobenzoyl chloride (255) was prepared[127] by reacting 2-chloro-5-nitrobenzoic acid with thionyl chloride, the product being collected after trituration with light petroleum rather than by distillation (94%), m.p. 58° (lit.,[127] 60°).

3,5-Dinitrobenzoyl chloride (243) was prepared[128] by reacting 3,5-dinitrobenzoic acid with phosphorus pentachloride (83%), m.p. 68° (from carbon tetrachloride) (lit.,[128] 68°).

3,5-Dinitro-2-methoxybenzoyl chloride (260) was prepared[132] by reacting 3,5-dinitro-2-methoxybenzoic acid with phosphorus pentachloride (78%), m.p. 38° (from carbon tetrachloride) (lit.,[132] 38°).

2-Chloro-3,5-dinitrobenzoyl chloride (248)

The reaction[132] of 2-chloro-3,5-dinitrobenzoic acid with thionyl chloride or phosphorus pentachloride gave 2-chloro-3,5-dinitrobenzoic anhydride (250) as an insoluble by-product (32%), m.p. 225° (from dioxan), $\nu_{max.}$ 1780, 1740 (CO), 1540 and 1350 (NO_2) cm^{-1},

Found: C,35.6; H,0.9; N,11.7%; M^+ 375.

$C_{14}H_4Cl_2N_4O_{11}$ requires: C,35.4; H,0.8; N,11.8%; M 375.

Work-up of the thionyl chloride or phosphorus pentachloride mother liquors gave 2-chloro-3,5-dinitrobenzoyl chloride (55%), m.p. 60° (lit.,[132] 62°).

N-Substituted α-Aminophenylacetonitriles (244a-c) were prepared by the method described by Spence and Tennant.[90] They had i.r. spectra identical to those of authentic samples and were used without further purification.

N-Benzyl α-aminophenylacetonitrile (244a) was obtained as a yellow oil (80%).

N-Phenyl α-aminophenylacetonitrile (244b) was obtained as a colourless solid (94%), m.p. 82° (lit.,[133] 85°).

N-Methyl α-aminophenylacetonitrile (244c) was obtained as a yellow oil (82%).

Preparation of N,N-Disubstituted Nitrobenzamides

The N-substituted α-aminophenylacetonitriles (244a-c) (0.04 mol) dissolved in anhydrous benzene (120 ml) were treated in one portion with solutions of the substituted benzoyl chlorides (251), (255), (243), (248) and (260) (0.02 mol) in anhydrous benzene (60 ml) and the mixtures

were stirred at room temperature for 15h. The insoluble amine hydrochlorides were collected and washed with benzene. The benzene washings and benzene filtrate were combined and evaporated under reduced pressure to give oils which solidified in contact with light petroleum to give the crude amides which were collected and purified by crystallisation.

α-(N-3-Nitrobenzoylanilino)phenylacetonitrile (238a) was obtained as pale yellow crystals (75%), m.p. 122° (from ethanol-light petroleum) (lit.,[91] 122°).

α-(N-Benzyl-N-3-nitrobenzoylamino)phenylacetonitrile (238b) formed fine colourless needles (97%), m.p. 119° (from methanol), $\nu_{max.}$ 1650 (CO), 1540 and 1350 (NO_2) cm^{-1},

Found:	C,70.8;	H,4.4;	N,11.7%.
$C_{22}H_{17}N_3O_3$ requires:	C,71.1;	H,4.6;	N,11.3%.

α-(N-Methyl-N-3-nitrobenzoylamino)phenylacetonitrile (238c) formed colourless crystals (98%), m.p. 113° (from methanol), $\nu_{max.}$ 1640 (CO), 1530 and 1360 (NO_2) cm^{-1},

Found:	C,65.5;	H,4.3;	N,14.1%.
$C_{16}H_{13}N_3O_3$ requires:	C,65.1;	H,4.4;	N,14.2%.

α-(N-3,5-Dinitrobenzoylanilino)phenylacetonitrile (241a) crystallised as pale yellow needles (90%), m.p. 166° (from glacial acetic acid) (lit.,[91] 166°).

α-(N-Benzyl-N-3,5-dinitrobenzoylamino)phenylacetonitrile (241b) formed colourless crystals (91%), m.p. 140° (from glacial acetic acid-ethanol), $\nu_{max.}$ 1660 (CO), 1550 and 1350 (NO_2) cm^{-1},

Found:	C,63.6;	H,3.7;	N,13.9%.
$C_{22}H_{16}N_4O_5$ requires:	C,63.5;	H,3.9;	N,13.5%.

α-(N-3,5-Dinitrobenzoyl-N-methylamino)phenylacetonitrile (241c) formed pale yellow crystals (89%), m.p. 160° (from glacial acetic acid-ethanol), $\nu_{max.}$ 1650 (CO), 1560 and 1350 (NO_2) cm^{-1},

Found:	C,56.1;	H,3.5;	N,16.1%.
$C_{16}H_{12}N_4O_5$ requires:	C,56.5;	H,3.6;	N,16.5%.

α-(N-2-Chloro-5-nitrobenzoylanilino)phenylacetonitrile (256a) crystallised as colourless needles (75%) m.p. 191° (from glacial acetic acid-ethanol) (lit.,[90] 191°).

α-(N-Benzyl-N-2-chloro-5-nitrobenzoylamino)phenylacetonitrile (256b) formed colourless crystals (90%), m.p. 146° (from ethanol), $\nu_{max.}$ 1650 (CO), 1540 and 1350 (NO_2) cm^{-1},

Found:	C,65.0;	H,4.4;	N,10.1%.
$C_{22}H_{16}ClN_3O_3$ requires:	C,65.1;	H,4.0;	N,10.4%.

α-(N-2-Chloro-5-nitrobenzoyl-N-methylamino)phenylacetonitrile (256c) was obtained as colourless crystals (94%), m.p. 144° (from ethanol), $\nu_{max.}$ 1640 (CO), 1540 and 1350 (NO_2) cm^{-1},

Found:	C,58.6;	H,4.0;	N,12.8%.
$C_{16}H_{12}ClN_3O_3$ requires:	C,58.3;	H,3.6;	N,12.8%.

α-(N-2-Chloro-3,5-dinitrobenzoylanilino)phenylacetonitrile (249a) formed pale yellow crystals (70%), m.p. 177° (ethanol-dimethylformamide), $\nu_{max.}$ 1680 (CO), 1560, 1550 and 1360 (NO_2) cm^{-1},

Found:	C,57.9;	H,3.1;	N,12.8%.
$C_{21}H_{13}ClN_4O_5$ requires:	C,57.7;	H,3.0;	N,12.8%.

α-(N-Benzyl-N-2-chloro-3,5-dinitrobenzoylamino)phenylaceto-nitrile (249b) formed pale yellow crystals (97%), m.p. 171° (from glacial acetic acid), $\nu_{max.}$ 1660 (CO), 1550 and 1350 (NO_2) cm^{-1},

Found:	C,58.6;	H,3.4;	N,12.2%.
$C_{22}H_{15}ClN_4O_5$ requires:	C,58.6;	H,3.3;	N,12.4%.

α-(N-2-Chloro-3,5-dinitrobenzoyl-N-methylamino)phenylacetonitrile (249c) was obtained as colourless crystals (83%), m.p. 143° (from glacial acetic acid-ethanol), $\nu_{max.}$ 1640 (CO), 1560, 1550 and 1350 (NO_2) cm^{-1},

Found:	C,51.2;	H,2.9;	N,14.4%.
$C_{16}H_{11}ClN_4O_5$ requires:	C,51.2;	H,2.9;	N,14.9%.

α-(N-3,5-Dinitro-2-methoxybenzoylanilino)phenylacetonitrile (258) formed pale yellow crystals (75%), m.p. 197° (from ethanol-dimethylformamide), $\nu_{max.}$ 1670 (CO), 1540 and 1350 (NO_2) cm^{-1}, τ [$(CD_3)_2SO$] 1.24 [1H, d, J_{meta} 2 Hz, H(4) or H(6)], 1.41 [1H, d, J_{meta} 2 Hz, H(6) or H(4)], 2.81 [11H, m, ArH + CH] and 6.02 [3H, s, Me],

Found:	C,61.5;	H,3.6;	N,13.2%.
$C_{22}H_{16}N_4O_6$ requires:	C,61.1;	H,3.7;	N,13.0%.

A solution of the amide (258) in dimethyl sulphoxide treated with triethylamine (0.1 ml) had $\lambda_{max.}$ 400 and 505 nm (log ε 4.04 and 3.86). The amide (258) (0.030g, 0.00007 mol) dissolved in [$(CD_3)_2SO$] and treated with triethylamine (0.003 ml, 0.00002 mol) had τ [$(CD_3)_2SO$] 1.24 [1H, d, J_{meta} 2 Hz, H(4) or H(6)], 1.41 [1H, d, J_{meta} 2 Hz, H(6) or H(4)], 1.59 (d, J 2 Hz), 1.84 (s), 1.99 (d, J 2 Hz), 2.81 (m, ArH) and 4.64 (s).

Base-Catalysed Reactions of N,N-Disubstituted 2-Chloro-5-nitrobenzamides (256a-c)

The amides (256a-c) (0.005 mol) in ethanol (300 ml) were heated under reflux with aqueous N-sodium carbonate (20.0 ml) until the initial red colour faded or for 1h. The mixture was evaporated under reduced pressure and the residue was treated with water. The solid obtained was collected and crystallised to yield the pure isoindolinones (239a-c).

1,2-Diphenyl-5-nitro-3-oxoisoindoline-1-carbonitrile (239a) crystallised as cream needles (81%), m.p. 224° (from glacial acetic acid-ethanol)(lit.,[90] 225°), τ [CF_3COOH] 1.01 [1H, d, J_{meta} 2 Hz, H(4)], 1.26 [1H, dd, J_{ortho} 9 Hz, J_{meta} 2 Hz, H(6)], 2.20 [1H, d, J_{ortho} 9 Hz, H(7)], 2.49-2.96 (10H,m,ArH).

2-Benzyl-5-nitro-3-oxo-1-phenylisoindoline-1-carbonitrile (239b) formed colourless crystals (92%), m.p. 158° (from glacial acetic acid-ethanol), $\nu_{max.}$ 1720 (CO), 1540 and 1360 (NO_2) cm^{-1}, τ [CF_3COOH] 1.07 [1H, d, J_{meta} 2 Hz, H(4)], 1.42 [1H, dd, J_{ortho} 9 Hz, J_{meta} 2 Hz, H(6)], 2.58 (11H,m, ArH), 4.72 (1H, d, J 15 Hz, CH) and 5.66 (1H, d, J 15 Hz, CH),

Found: C,71.7; H,4.1; N,11.4%; M^+ 369.

$C_{22}H_{15}N_3O_3$ requires: C,71.5; H,4.1; N,11.4%; M 369.

2-Methyl-5-nitro-3-oxo-1-phenylisoindoline-1-carbonitrile (239c) formed colourless needles (90%), m.p. 158° (from ethanol), $\nu_{max.}$ 1720 (CO), 1550 and 1360 (NO_2) cm^{-1}, τ [$CDCl_3$] 1.27 [1H, d, J_{meta} 2 Hz, H(4)], 1.55 [1H, dd, J_{ortho} 9 Hz, J_{meta} 2 Hz, H(6)], 2.57 (6H, m, ArH) and 6.96 (3H, s, Me),

Found: C,65.1; H,4.3; N,13.7%; M^+ 293.

$C_{16}H_{11}N_3O_3$ requires: C,65.5; H,3.8; N,14.3%; M 293.

Base-Catalysed Reactions of N,N-Disubstituted 2-Chloro-3,5-dinitrobenzamides (249a-c)

(a) The amides (249a-c) (0.002 mol) in ethanol (120 ml) were heated under reflux with either aqueous N-sodium carbonate (8.0 ml) or aqueous N-sodium acetate (8.0 ml). The mixtures were evaporated under reduced pressure and the residues were treated with water. The Solids (A) were collected and the aqueous filtrates were extracted with chloroform. In no case was any material recovered from the chloroform extract.

(b) The amides (249b and c) (0.002 mol) in ethanol (150 ml) were heated under reflux with aniline (0.5 ml, 0.005 mol) for 15 min. The mixtures were cooled and acidified with dilute aqueous hydrochloric acid and the solvent was removed by distillation under reduced pressure. The residues were treated with water and the solids obtained were collected and crystallised to give the pure phthalimidines.

α-(N-2-Chloro-3,5-dinitrobenzoylanilino)phenylacetonitrile (249a)

(1) Reaction with aqueous ethanolic sodium carbonate under reflux for 1h gave a Solid (A) (0.7g) which was shown by t.l.c. in ether over silica to be a non-resolvable mixture of five components.

(2) Reaction with aqueous ethanolic sodium carbonate under reflux for 2 min gave a rust coloured Solid (A) (0.7g) which was shown by t.l.c. in benzene over silica to be a mixture of three components. The product (A) was leached with

ethanol giving an insoluble cream coloured solid (0.6g) which was crystallised to yield the pure phthalimidine (242a) more of which was obtained by evaporating the ethanol filtrate and trituration with ether (total 0.4g, 48%).

(3) Reaction with aqueous ethanolic sodium acetate under reflux for 4 min gave a Solid (A) (0.7g) which was crystallised to afford the pure phthalimidine (242a) (95%).

5,7-Dinitro-1,2-diphenyl-3-oxoisoindoline-1-carbonitrile (242a) formed pale yellow rhombic crystals, m.p. 226° (from glacial acetic acid-ethanol), $\nu_{max.}$ 1720 (CO), 1560, 1550 and 1360 (NO_2) cm^{-1}, τ [CF_3COOH] 0.56 [1H, d, J_{meta} 2 Hz, H(4) or H(6)], 0.73 [1H, d, J_{meta} 2 Hz, H(6) or H(4)] and 2.80 (10H, m, ArH),

Found: C,63.0; H,2.9; N,14.0%; M^+ 400.

$C_{21}H_{12}N_4O_5$ requires: C,63.0; H,3.0; N,14.0%; M 400.

α-(N-Benzyl-N-2-chloro-3,5-dinitrobenzoylamino)phenylacetonitrile (249b)

(1) Reaction with aqueous ethanolic sodium carbonate under reflux for 5 min gave a Solid (A) (0.9g) which was shown by t.l.c. in ether over silica to be a mixture of four components. Chromatography in benzene over alumina gave the phthalimidine (242b) (0.1g, 13%). Further elution gave small amounts of unidentified solids (total 0.02g).

(2) Reaction with aqueous ethanolic sodium acetate under reflux for 5 min gave a red-brown Solid (A) (0.7g) which was crystallised (charcoal) to afford the pure phthalimidine (242b) (70%).

(3) Reaction with aniline in ethanol under reflux gave the pure phthalimidine (242b) (77%).

2-Benzyl-5,7-dinitro-3-oxo-1-phenylisoindoline-1-carbonitrile (242b) had m.p. 179° (from glacial acetic acid-ethanol), $\nu_{max.}$ 1720 (CO), 1550 and 1360 (NO_2) cm^{-1}, τ [CF_3COOH] 0.66 [1H, d, J_{meta} 2 Hz, H(4) or H(6)], 0.72 [1H, d, J_{meta} 2 Hz, H(6) or H(4)], 2.73 (10H, m, ArH), 4.92 (1H, d, J 14 Hz, CH) and 5.56 (1H, d, J 14 Hz, CH),

Found: C,63.7; H,3.4; N,13.4%; M^+ 414.

$C_{22}H_{14}N_4O_5$ requires: C,63.8; H,3.4; N,13.5%; M 414.

α-(N-2-Chloro-3,5-dinitrobenzoyl-N-methylamino)phenylacetonitrile (249c)

(1) Reaction with aqueous ethanolic sodium acetate under reflux for 5 min gave a Solid (A) (0.7g) which was shown by t.l.c. in ether over silica to be a mixture. Leaching with benzene gave an insoluble solid (0.05g) which was not characterised. Evaporation of the benzene filtrate afforded the phthalimidine (242c) (0.6g, 82%).

(2) Reaction with aniline in ethanol under reflux gave the pure phthalimidine (242c) (79%).

5,6-Dinitro-2-methyl-3-oxo-1-phenylisoindoline-1-carbonitrile (242c) formed colourless crystals, m.p. 176° (from glacial acetic acid-ethanol), $\nu_{max.}$ 1720 (CO), and 1560 and 1530 (NO_2) cm^{-1}, τ [CF_3COOH] 0.65 [1H, d, J_{meta} 2 Hz, H(4) or H(6)], 0.75 [1H, d, J_{meta}, H(6) or H(4)], 2.59 (5H, m, ArH) and 6.87 (3H, s, Me),

Found: C,57.1; H,3.0; N,16.4%; M^+ 338.

$C_{16}H_{10}N_4O_5$ requires: C,56.8; H,3.0; N,16.6%; M 338.

Base-Catalysed Reactions of N,N-Disubstituted 3,5-dinitrobenzamides (241a-c)

α-(N-3,5-Dinitrobenzoylanilino)phenylacetonitrile (241a)

(a) The amide (241a) (0.8g, 0.002 mol) dissolved in ethanol (200 ml) was treated with aqueous N-sodium carbonate solution (8.0 ml). The deep red reaction mixture was stirred at room temperature for 1.5h and was then evaporated under reduced pressure. The residue was treated with water to give a solid (0.6g) which was shown by t.l.c. in benzene over silica to be an unresolvable mixture of four components. The i.r. spectrum, $\nu_{max.}$ 3300br (NH) and 1720br (CO) cm^{-1}, of the mixture indicated the presence of the nitrile (242a) and the amide derived by hydrolysis. Extraction of the aqueous mother liquors with chloroform gave no further material.

(b) The amide (241a) (0.8g, 0.002 mol) in ethanol (200 ml) was heated under reflux with aqueous N-sodium acetate (8.0 ml) for 1h. The mixture was evaporated and the residue was treated with water to give a solid which was collected and crystallised to yield the phthalimidine (242a) (62%), identical (m.p. and i.r. spectrum) to a sample prepared previously.

(c) The amide (241a) (0.8g, 0.002 mol) in ethanol (200 ml) was treated with benzoquinone (0.2g, 0.002 mol) followed by aqueous N-sodium acetate (8.0 ml). The red reaction mixture was heated under reflux for 20 min. The solvent was evaporated and the residue was treated with water to give a light brown solid, crystallisation of which gave the phthalimidine (242a) (92%), identical (m.p. and i.r. spectrum) to a sample prepared previously.

(d) The amide (241a) (0.4g, 0.001 mol) in ethanol (100 ml) was treated with triethylamine (0.15 ml, 0.002 mol) and N-bromosuccinimide (0.16g, 0.001 mol) at room temperature. On cooling (-15°) a colourless solid was collected (0.3g) and identified as the starting amide (i.r. spectrum). The filtrate was evaporated to a gummy solid which on trituration with ether gave a colourless solid (0.1g) whose i.r. spectrum had no well-defined absorptions and which was not further investigated.

α-(N-Benzyl-N-3,5-dinitrobenzoylamino)phenylacetonitrile (241b)

(a) The amide (241b) (6.2g, 0.015 mol) in ethanol (1000 ml) was heated under reflux with aqueous N-sodium acetate (60.0 ml) for 20 min. The mixture was evaporated and the residue was treated with water to give a yellow solid (5.8g) which was chromatographed over alumina. Elution with toluene-ether (5:1) gave the pure phthalimidine (242b) (1.0g) identified by comparison (m.p. and i.r. spectrum) with a sample obtained previously. Further elution with the same solvent gave a red solid (1.6g) which was shown by t.l.c. in ether over silica to be a mixture of the phthalimidine (242b) and two other components. Elution with solvents of increasing polarity produced further mixtures. The mixtures were combined (total weight 3.1g) and re-chromatographed over alumina. Elution with toluene gave the phthalimidine (242b) (0.94g) identical (m.p. and i.r. spectrum) to a sample previously obtained. The total yield of phthalimidine (242b) was (1.9g, 31%).

(b) The amide (241b) (0.8g, 0.002 mol) dissolved in ethanol (200 ml) was treated with benzoquinone (0.2g, 0.002 mol)

followed by aqueous N-sodium acetate (8.0 ml). The red reaction mixture was heated under reflux for 20 min and the solvent was then evaporated. Treatment of the residue with water gave a light brown solid, crystallisation of which afforded the phthalimidine (242b) (0.7g, 91%), m.p. 179° (from glacial acetic acid-ethanol) identical (m.p. and i.r. spectrum) to a sample previously obtained.

α-(N-3,5-Dinitrobenzoyl-N-methylamino)phenylacetonitrile (241c)

The amide (241c) (0.7g, 0.002 mol) in ethanol (200 ml) was treated with benzoquinone (0.2g, 0.002 mol) followed by aqueous N-sodium acetate (8.0 ml). The red reaction mixture was heated under reflux for 20 min. The solvent was evaporated under reduced pressure and the residue was treated with water to give a light brown solid, crystallisation of which gave the phthalimidine (242c) (95%), m.p. 176°, identical (m.p. and i.r. spectrum) to a sample obtained previously.

Base-Catalysed Reactions of N,N-Disubstituted 3-Nitrobenzamides (238a-c)

α-(N-3-Nitrobenzoylanilino)phenylacetonitrile (238a)

(a) The amide (238a) (3.6g, 0.01 mol) dissolved in ethanol (300 ml) was stirred for 1h at room temperature with aqueous N-sodium acetate (40.0 ml). The mixture was evaporated under reduced pressure and the residue was treated with water to afford the starting amide (238a)(quantitative).

(b) The amide (238a) (3.6g, 0.01 mol) dissolved in ethanol (300 ml) was heated under reflux for 2.5h with aqueous N-sodium acetate (40.0 ml). Evaporation of the mixture under reduced pressure and treatment of the residue with water gave

a solid (3.4g) whose t.l.c. in benzene over alumina showed it to be a mixture of three components. Chromatography in benzene over alumina gave the 5-nitrophthalimidine (239a) (0.97g) m.p. 223° (from glacial acetic acid) (lit.,[134] 225°). Further elution with benzene gave the 7-nitrophthalimidine (240a) (0.05g), m.p. 212° (from glacial acetic acid) (lit.,[134] 214°).

α-(N-Benzyl-3-nitrobenzoylamino)phenylacetonitrile (238b)

The amide (238b) (3.7g, 0.01 mol) dissolved in ethanol (300 ml) was treated with benzoquinone (1.1g, 0.01 mol) followed by aqueous N-sodium acetate (40.0 ml). The reaction mixture was heated under reflux for 20 min then the solvent was evaporated under reduced pressure. The residue was treated with water giving a brown solid (3.5g) whose t.l.c. in benzene-ether (4:1) indicated a mixture of two main components. Chromatography in toluene over alumina gave the 5-nitrophthalimidine (239b) (1.5g) m.p. 158°. Further elution with toluene gave a yellow oil (1.6g) shown by t.l.c. in benzene-ether (4:1) over silica to be a mixture of the 5-nitrophthalimidine (239b) and one other compound. The column yielded no further material. The yellow oil was re-chromatographed over alumina and elution with toluene gave the 5-nitrophthalimidine (239b) (0.1g). Further elution with toluene gave a yellow oil (1.4g) which was re-chromatographed in light petroleum-toluene (5:1) over alumina to give the 5-nitrophthalimidine (239b) (0.8g). Further elution with the same solvent mixture afforded the 7-nitrophthalimidine (240b) (0.3g). The total yield of the 5-nitrophthalimidine (239b) was (2.4g, 65%) and was identical (m.p. and i.r. spectrum)

with a sample obtained previously. 2-Benzyl-7-nitro-3-oxo-isoindoline-1-carbonitrile (240b) formed colourless crystals (8%) m.p. 148° (from glacial acetic acid-ethanol), $\nu_{max.}$ 1720 (CO), 1530 and 1360 (NO_2) cm^{-1}, τ [$CDCl_3$] 1.54 [1H, dd, J_{ortho} 9 Hz, J_{meta} 2 Hz, H(4) or H(6)], 1.62 [1H, dd, J_{ortho} 9 Hz, J_{meta} 2 Hz, H(6) or H(4)], 2.11 [1H, dd, J_{ortho} 9 Hz, H(5)], 2.80 (10H, m, ArH), 5.38 (1H, d, J 15 Hz, CH) and 5.96 (1H, d, J 15 Hz, CH),

Found: C,71.5; H,4.1; N,11.1%; M^+ 369.

$C_{22}H_{15}N_3O_3$ requires: C,71.5; H,4.1; N,11.4%; M 369.

α-(N-Methyl-3-nitrobenzoylamino)phenylacetonitrile (238c)

The amide (238c) (5.9g, 0.02 mol) dissolved in ethanol (300 ml) was treated with benzoquinone (2.2g, 0.02 mol) followed by aqueous N-sodium acetate (40.0 ml). The reaction mixture was heated under reflux for 20 min then evaporated under reduced pressure. The residue was treated with water and the solid obtained was collected (5.6g) and shown by t.l.c. in benzene-ether (4:1) over silica to be a mixture of two components. Chromatography in light petroleum-toluene (4:1) over alumina gave the 5-nitrophthalimidine (239c) (1.8g) m.p. 158°, identified by comparison (m.p. and i.r. spectrum) with a sample prepared previously. Further elution with the same solvent mixture gave a solid (2.4g) whose t.l.c. in benzene-ether (4:1) over silica indicated a mixture of the 5-nitrophthalimidine (239c) and one other component. This mixture was subjected to dry-column chromatography in ether over alumina giving more of the pure 5-nitrophthalimidine (239c) (0.5g) and a solid (0.9g) whose t.l.c. indicated that

it was a mixture of the 5-nitrophthalimidine (239c) and a second component. This two component mixture was subjected to repeated high speed liquid chromatography in dioxan-n-hexane (3:7) over alumina to give the pure 5-nitrophthalimidine (239c) and 2-methyl-7-nitro-3-oxo-1-phenylisoindoline-1-carbonitrile (240c), m.p. 195°, $\nu_{max.}$ 1710 (CO), 1540 and 1340 (NO_2) cm^{-1}, τ [$CDCl_3$] 1.54 [1H, dd, J_{ortho} 9 Hz, J_{meta} 2 Hz, H(4) or H(6)], 1.66 [1H, dd, J_{ortho} 9 Hz, J_{meta} 2 Hz, H(6) or H(4)], 2.11 [1H, t, J_{ortho} 9 Hz, H(5)], 2.56-2.80 (5H, m, ArH) and 7.07 (3H, s, Me),

Found: C,64.6; H,3.9; N,14.4%; M^+ 293.

$C_{16}H_{11}N_3O_3$ requires: C,65.5; H,3.8; N,14.3%; M 293.

The Attempted Preparation of 1,2-Diphenyl-5-nitro-3-oxoisoindoline-1-carboxamide (252)

(a) 1,2-Diphenyl-5-nitro-3-oxoisoindoline-1-carbonitrile (239a) (0.1g) dissolved in ethanol (6.0 ml) was heated under reflux for 2h with aqueous N-sodium carbonate (2.0 ml). The mixture was evaporated under reduced pressure and the residue was treated with water and was filtered to give a colourless solid (0.08g) whose t.l.c. in ether over silica showed it to be an unresolvable mixture of three components, which was not examined further.

(b) The cyanophthalimidine (239a) (0.1g) dissolved in ethanol (13.0 ml) was heated under reflux for 1.5h with 30% w/v aqueous sulphuric acid (1.0 ml). The cooled mixture was evaporated and the residue was treated with water to give unreacted starting material (0.09g, 90%) identical (m.p. and i.r. spectrum) to an authentic sample.

The reaction was repeated using glacial acetic acid, instead of ethanol, as solvent but again only starting material (quantitative) was recovered.

(c) The cyanophthalimidine (239a) (0.08g) was heated at 100° for 2h with polyphosphoric acid (1.0g). The solution was diluted with water (30 ml) and the resulting colourless solid was collected (0.03g). T.l.c. in ether over silica indicated a multi-component mixture which was not investigated further.

2.8. The Attempted Base-Catalysed Cyclisation of Mandelonitrile 2-Chloro-3,5-dinitrobenzoate

α-Cyanobenzyl 2-Chloro-3,5-dinitrobenzoate (274)

A solution of potassium cyanide (0.7g) in water (6.0 ml) was treated with benzaldehyde (1.1g, 0.01 mol) and 2-chloro-3,5-dinitrobenzoyl chloride (248) (2.7g, 0.01 mol) and the mixture was stirred at room temperature for 15h. The reaction mixture was treated with water and chloroform and the chloroform layer was washed successively with saturated aqueous sodium hydrogen sulphite and saturated aqueous sodium hydrogen carbonate and was evaporated to give the product (274) (2.9g, 81%), m.p. 106° (from ethanol), $\nu_{max.}$ 1720 (CO), 1550 and 1360 (NO_2) cm^{-1},

Found:	C,50.3;	H,2.2;	N,11.6%.
$C_{15}H_8ClN_3O_6$ requires:	C,49.8;	H,2.2;	N,11.7%.

The Attempted Cyclisation of the Ester (274)

The ester (274) (0.7g, 0.002 mol) in ethanol (30 ml) was heated under reflux for 5 min with aqueous N-sodium acetate (8.0 ml). The cooled reaction mixture was evaporated to give an oil which was treated with water and chloroform. Evaporation of the chloroform layer gave a red gum (0.5g) whose t.l.c. in benzene-ether (1:1) over silica indicated a multi-component mixture which was not further investigated.

2.9. The Attempted Base-catalysed Cyclisation of 2-Nitrobenzoylhydrazines

Benzylidenephenylhydrazine was prepared[135] by the reaction of phenylhydrazine with benzaldehyde (94%), m.p. 151° (from ethanol) (lit.,[135] 153°).

2-Benzylidene-1-(2-nitrobenzoyl)-1-phenylhydrazine (282)

Benzylidenephenylhydrazine (15.7g, 0.08 mol) was dissolved in pyridine (22.0 ml, 0.24 mol) and anhydrous benzene (65 ml). 2-Nitrobenzoyl chloride (14.7g, 0.08 mol) dissolved in anhydrous benzene (55 ml) was added dropwise and the mixture was stirred at room temperature for 48h. The insoluble pyridine hydrochloride was filtered off, the benzene was washed with dilute aqueous hydrochloric acid (2 x 100 ml) and the benzene was evaporated to give a yellow solid which was crystallised to afford the product (282) (19.1g, 69%), m.p. 135° (from ethanol) (lit.,[104] 137°).

The Attempted Hydrolysis of 2-Benzylidene-1-(2-nitrobenzoyl)-1-phenylhydrazine (282)

(a) The hydrazone (282) (1.1g, 0.003 mol) dissolved in ethanol (25.0 ml) was saturated with hydrogen chloride and left at room temperature for 15h. The mixture was evaporated under reduced pressure to yield starting material (1.0g), identical (m.p. and i.r. spectrum) with an authentic sample.

(b) The hydrazone (282) (0.7g, 0.007 mol) dissolved in ethanol (20.0 ml) was heated at 100° for 1.5h with dilute aqueous sulphuric acid (10.0 ml). The solution was concentrated under reduced pressure (ca. 10 ml) and filtered to give the starting

hydrazone (0.67g), identical (m.p. and i.r. spectrum) with an authentic sample.

(c) A solution of the hydrazone (282) (1.1g, 0.003 mol) in ethanol (35 ml) was heated under reflux for 1h with 20% w/v aqueous potassium hydroxide (10.0 ml). The mixture was evaporated under reduced pressure and the residue was treated with water. Filtration gave benzylidenephenylhydrazine (0.5g) identical (m.p. and i.r. spectrum) with an authentic sample. The aqueous alkaline filtrate was acidified with dilute aqueous hydrochloric acid and was then extracted with chloroform. The chloroform extract was washed with saturated aqueous sodium hydrogen carbonate and the washings were acidified to yield 2-nitrobenzoic acid (0.3g) identical (m.p. and i.r. spectrum) with an authentic sample. The chloroform on work-up gave a negligible amount of gum.

Acetaldehyde phenylhydrazone was prepared by reacting[136] phenylhydrazine with acetaldehyde (54%), m.p. 88° (from ethanol) (lit.,[136] 98°).

2-Ethylidene-1-(2-nitrobenzoyl)-1-phenylhydrazone (283)

Acetaldehyde phenylhydrazone (6.7g, 0.05 mol) dissolved in pyridine (12.0 ml) and anhydrous benzene (40 ml) was treated with a solution of 2-nitrobenzoyl chloride (9.3g, 0.05 mol) in anhydrous benzene (40 ml) and the mixture was stirred at room temperature for 48h. The insoluble pyridine hydrochloride was filtered off, the benzene was washed with dilute aqueous hydrochloric acid (2 x 75 ml) and was evaporated to give a red gum (11.3g). T.l.c. of this gum in ether over silica indicated that it was a mixture consisting

of one main component and five minor components. Chromatography in toluene-ether (4:1) over alumina afforded 2-ethylidene-1-(2-nitrobenzoyl)-1-phenylhydrazine (283) (9.1g, 65%), m.p. 110° (from ethyl acetate-light petroleum), $\nu_{max.}$ 1670 (CO), 1620 (C=C), 1530 and 1360 (NO_2) cm^{-1}, τ [$CDCl_3$] 1.90 (1H, dd, J_{ortho} 9 Hz, J_{meta} 2 Hz, ArH), 2.38-2.76 (8H,m,ArH), 3.37 (1H, q, J 5 Hz, CH) and 8.37 (3H, d, J 5 Hz, Me),

Found:	C,63.7;	H,4.5;	N,15.0%.
$C_{15}H_{13}N_2O_3$ requires:	C,63.6;	H,4.6;	N,14.8%.

The Attempted Hydrolysis of 2-Ethylidene-1-(2-nitrobenzoyl)-1-phenylhydrazine (283)

A solution of the hydrazone (283) (0.8g, 0.003 mol) in ethanol (25.0 ml) was saturated with hydrogen chloride and was left at room temperature for 15 h. The mixture was evaporated under reduced pressure to give a solid (0.8g) whose i.r. spectrum [$\nu_{max.}$ 2600br (NH), 1680 (CO), 1520 and 1340 (NO_2) cm^{-1}] indicated that it was a hydrochloride. The solid was treated with saturated aqueous sodium hydrogen carbonate and was extracted into chloroform to give a gum (0.5g) whose t.l.c. in ether-toluene (4:1) showed it to be a multi-component mixture which was not further investigated.

1-Methyl-1-(2-nitrobenzoyl)hydrazine (284)

A solution of methylhydrazine (1.8g, 0.04 mol) in anhydrous benzene (25.0 ml) was added dropwise with stirring to a solution of 2-nitrobenzoyl chloride (3.7g, 0.02 mol) in anhydrous benzene (25.0 ml) and the mixture was stirred at room temperature for 12h. The insoluble methylhydrazine hydrochloride was filtered off and the benzene filtrate was

evaporated under reduced pressure to give 1-methyl-1-(2-nitro benzoyl)hydrazine (284)(2.9g, 75%) m.p. 102° (from ethanol-light petroleum), $\nu_{max.}$ 3300, 3200 (NH_2), 1660 (CO) and 1610 (NH def.), τ [CF_3COOH] 1.55 (1H, dd, J_{ortho} 9 Hz, J_{meta} 2 Hz, ArH), 1.99-2.38 (3H,m,ArH) and 6.50 (3H,s,Me),

Found:	C,49.2;	H,4.7;	N,21.5%.
$C_8H_9N_3O_3$ requires:	C,49.5;	H,4.6;	N,21.9%.

Base-Catalysed Reactions of 1-Methyl-1-(2-nitrobenzoyl) hydrazine (284)

(a) The hydrazide (284) (0.9g, 0.005 mol) was heated under reflux with 20% w/v aqueous potassium hydroxide (4.0 ml) for 0.5h. Extraction of the cooled reaction mixture with chloroform gave no material. The aqueous alkaline phase was acidified with dilute aqueous hydrochloric acid and the gummy solid produced was extracted into chloroform. The chloroform extract was washed with saturated aqueous sodium hydrogen carbonate and the washings were acidified to give a gum which on trituration with benzene afforded an unidentified carboxylic acid, (0.04g) m.p. 241° (from ethanol), $\nu_{max.}$ 2650, 2550 (OH), 1690 (CO) cm^{-1}, M^+ 269. The chloroform layer gave no further material.

(b) The hydrazide (284) (0.9g, 0.005 mol) was heated under reflux with aqueous N-sodium carbonate (8.0 ml) for 0.5h. The reaction mixture was extracted with chloroform to give the starting hydrazide (284) (0.7g), identical (m.p. and i.r. spectrum) to an authentic sample. The aqueous phase was acidified with dilute aqueous hydrochloric acid to give a red gum (0.1g) whose t.l.c. in ether over silica indicated an unresolvable three component mixture which was not further investigated.

(c) The hydrazide (284) (0.9g, 0.005 mol) dissolved in absolute ethanol (20.0 ml) was heated under reflux for 1h with a solution of sodium (0.5g, 0.02 mol) in absolute ethanol (18.0 ml). The mixture was evaporated under reduced pressure and the residue was treated with water and chloroform. The chloroform phase gave no material and acidification of the aqueous alkaline phase with dilute aqueous hydrochloric acid gave a gum which was extracted into chloroform. The chloroform extract was washed with saturated aqueous sodium hydrogen carbonate and the washings were acidified to give a red gum (0.2g) whose t.l.c. in ether over silica showed it to be an unresolvable mixture of four components which was not further investigated. The chloroform extract gave no material.

2.10 The Base-Catalysed Cyclisation of 2-Nitrobenzoylacetylacetone. A Novel 3-Hydroxyquinoline Synthesis.

2-Nitrobenzoyl chloride was prepared as described before (see page 91).

2-Nitrobenzoylacetylacetone (296) and its sodium salt (297)

(a) The condensation of 2-nitrobenzoyl chloride with acetylacetone by the method of Loudon and Wellings[49] gave the sodium salt (297) of 2-nitrobenzoylacetylacetone (yield 60%) (contaminated with sodium chloride) which on treatment with mineral acid afforded 2-nitrobenzoylacetylacetone (296) (57%), m.p. 70° (from ethanol) (lit.,[49] 72°).

(b) Absolute ethanol (5.0 ml) and carbon tetrachloride (0.5 ml) were added to magnesium turnings (5.4g, 0.022 mol). Anhydrous ether (150 ml) was added after 2 min, followed by a solution of acetylacetone (22g, 0.22 mol) in absolute ethanol (20 ml) and anhydrous ether (25 ml) at a rate which maintained boiling. The reaction mixture was heated under reflux for 5h by which time most of the magnesium had reacted. A solution of 2-nitrobenzoyl chloride (37g, 0.2 mol) in anhydrous ether (50 ml) was added over 15 min and heating under reflux was continued for 45 min. Dilute aqueous sulphuric acid (225 ml) was added to the cooled reaction mixture. The ether layer was separated and evaporated to give a gummy solid (44.6g) whose t.l.c. in benzene-ether (3:2) over silica showed it to be a mixture of a major and a minor component. Chromatography in chloroform over silica gave the product (296) (23.1g, 42%), m.p. 70° (from ethanol)(lit.,[49] 72°). No further pure material was obtained from the column.

2-Acetyl-3-hydroxyquinoline (311)

2-Nitrobenzoylacetylacetone (296) (12.5g, 0.05 mol) or the sodium salt (297) of 2-nitrobenzoylacetylacetone (16.4g) (containing 20% by weight of sodium chloride) in ethanol (100 ml) was heated under reflux with 20% w/v potassium hydroxide (50 ml) for 30 min. The cooled reaction mixture was evaporated under reduced pressure and the red oily residue was treated with water and neutralised with dilute aqueous hydrochloric acid. Carbon dioxide was evolved and the yellow solid was collected, washed with water and crystallised to give the pure quinoline (311) (7.8g, 83%), m.p. 118° (from ethanol), $\nu_{max.}$ 1650 (CO) cm^{-1}, $\lambda_{max.}$ 211, 241, 309 and 375 nm (log ε 4.32, 4.56, 3.91 and 3.50), τ [$CDCl_3$] -1.16 (1H,s,OH), 1.90-2.52 (5H,m,ArH) and 7.09 (3H,s,Me). The signal at τ -1.16 disappeared after shaking with D_2O.

Found:	C,70.6;	H,4.9;	N,7.3%;	M^+ 187.
$C_{11}H_9NO_2$ requires:	C,70.6;	H,4.8;	N,7.5%;	M 187.

3-Acetoxy-2-acetylquinoline (337)

2-Acetyl-3-hydroxyquinoline (311) (0.9g, 0.004 mol) was heated under reflux in acetic anhydride (2.5 ml) for 15 min. The mixture was allowed to cool and was left at room temperature for 20 min. The excess of acetic anhydride was evaporated under reduced pressure and the residue was triturated with ether to afford the acetoxy derivative (337) (0.7g, 80%), m.p. 80° (from light petroleum), $\nu_{max.}$ 1750 and 1690 (CO) cm^{-1}, τ [$CDCl_3$] 1.73-2.42 (5H,m,ArH), 7.18 (3H,s,Me) and 7.60 (3H,s,Me),

Found: C,68.7; H,4.8; N,6.1%; M^+ 229.

$C_{13}H_{11}NO_3$ requires: C,68.1; H,4.8; N,6.1%; M 229.

The Alkaline Hydrolysis of 3-Acetoxy-2-acetylquinoline (337)

The acetoxy derivative (337) (0.1g) was dissolved in the minimum volume (ca. 1 ml) of 10% w/v aqueous sodium hydroxide. The yellow solution was neutralised with dilute aqueous hydrochloric acid and the yellow crystals were collected to yield 2-acetyl-3-hydroxyquinoline (0.08g), identical (m.p. and i.r. spectrum) with an authentic sample.

3-Acetoxy-2-(α-hydroxyethyl)quinoline (340)

(a) 3-Acetoxy-2-acetylquinoline (337) (0.6g, 0.003 mol) dissolved in ethanol (75 ml) was hydrogenated at room temperature and atmospheric pressure over 10% palladium-on-charcoal (0.1g). Filtration and evaporation of the ethanol under reduced pressure gave a solid which was crystallised to yield 3-acetoxy-2-(α-hydroxyethyl)quinoline(340) (0.5g, 83%).

(b) 3-Acetoxy-2-acetylquinoline (337) (0.6g, 0.003 mol) dissolved in 70% v/v aqueous ethanol (30 ml) was heated under reflux with sodium dithionite (0.6g) for 1h and then for a further 1h with a second portion (0.6g) of sodium dithionite. The cooled reaction mixture was evaporated under reduced pressure and the residue was treated with water (20 ml) and chloroform (30 ml). Evaporation of the chloroform extract gave 3-acetoxy-2-(α-hydroxyethyl)quinoline (340) (0.4g, 70%) as colourless needles, m.p. 181° (from ethanol), $\nu_{max.}$ 2700br (OH) and 1730 (CO) cm^{-1}, τ [CF_3COOH] 1.47 (1H,s, ArH), 1.66-2.13 (4H,m,ArH), 3.24 (1H, q, J 7 Hz, CH), 7.58

(3H,s,Me) and 8.08 (3H,d,J 7 Hz, Me),

Found: C,67.6; H,5.8; N,6.1%; M^+ 231.

$C_{13}H_{13}NO_3$ requires: C,67.5; H,5.6; N,6.1%; M 231.

2-(α-Hydroxyethyl)-3-hydroxyquinoline (338)

(a) 2-Acetyl-3-hydroxyquinoline (311) (0.6g, 0.003 mol) dissolved in ethanol (75 ml) was hydrogenated at room temperature and at atmospheric pressure over 10% palladium-on-charcoal. Filtration and evaporation of the ethanol under reduced pressure gave an oil which, on scratching, yielded a solid whose t.l.c. in ether over silica indicated a mixture of the starting material and one other component. The solid was redissolved in ethanol (75 ml) containing a few drops of glacial acetic acid and was re-hydrogenated to yield 2-(α-hydroxyethyl)-3-hydroxyquinoline (338) (0.5g, 80%).

(b) 2-Acetyl-3-hydroxyquinoline (311) (0.6g, 0.003 mol) in 70% v/v aqueous ethanol (30 ml) was heated under reflux with sodium dithionite (0.6g) for 1h and then for a further 1h with a second portion (0.6g) of sodium dithionite. The cooled reaction mixture was evaporated under reduced pressure and the residue was treated with water (20 ml) and chloroform (30 ml). Evaporation of the chloroform extract gave a yellow-green gum which solidified on trituration with ether and was crystallised to yield sand coloured plates of 2-(α-hydroxyethyl)-3-hydroxyquinoline (338) (0.4g, 70%) m.p. 134° (from aqueous methanol), $\nu_{max.}$ 3200br (OH) cm^{-1}, $\lambda_{max.}$ 213, 233, 317 and 330 nm (log ε 4.60, 4.48, 3.71 and 3.78), τ [$(CD_3)_2CO$] 2.01-2.62 (5H,m,ArH), 4.78 (1H, q, J 7 Hz, CH) and 8.45 (3H, d, J 7 Hz, Me),

Found: C,69.7; H,6.0; N,7.5%; M^+ 189.

$C_{11}H_{11}NO_2$ requires: C,69.8; H,5.9; N,7.4%; M 189.

2-(α-Acetoxyethyl)-3-acetoxyquinoline (339)

(a) 3-Acetoxy-2-(α-hydroxyethyl)quinoline (340) (0.23g, 0.001 mol) was heated very briefly over a Bunsen flame with acetic anhydride (ca. 1 ml) giving a red-brown solution. The mixture was allowed to cool and then was left at room temperature for 20 min. The excess of acetic anhydride was evaporated under reduced pressure to give a gum from which no solid could be obtained by trituration. The gum was left in contact with water for 3h and was then extracted with chloroform. The chloroform extract gave, after washing with saturated aqueous sodium hydrogen carbonate, a gum which afforded a light brown solid on trituration with light petroleum. Crystallisation gave colourless needles of the diacetoxyquinoline (339) (0.16g, 60%).

(b) Acetylation of 2-(α-hydroxyethyl)-3-hydroxyquinoline (338) (0.19g, 0.001 mol) as described in (a) above gave colourless needles of 2-(α-acetoxyethyl)-3-acetoxyquinoline (339) (0.26g, 97%), m.p. 60° (from light-petroleum b.p. 40-60°), $\nu_{max.}$ 1780 and 1730 (CO) cm^{-1}, τ [$CDCl_3$] 1.94-2.61 (5H,m,ArH), 3.71 (1H, q, J 7 Hz, CH), 7.62 (3H,s,Me), 7.96 (3H,s,Me) and 8.30 (3H, d, J 7 Hz, Me),

Found:	C,65.5;	H,5.5;	N,5.1%;	M^+ 273.
$C_{15}H_{15}NO_4$ requires:	C,65.9;	H,5.5;	N,5.1%;	M 273.

Oxidation Reactions of 2-Acetyl-3-Hydroxyquinoline (311)

(a) Using Chromium Trioxide

2-Acetyl-3-hydroxyquinoline (311) (0.1g) in 70% v/v aqueous acetic acid (10.0 ml) was heated at 100° with chromium trioxide (0.2g) for 0.5h. The very dark mixture was evaporated

under reduced pressure and the residue was treated with water to give an intractable green inorganic solid (0.1g) from which no identifiable material could be obtained. Extraction of the aqueous phase with chloroform gave no further material.

(b) Using Sodium Dichromate

(i) 2-Acetyl-3-hydroxyquinoline (311) (0.9g, 0.005 mol) dissolved in glacial acetic acid (40 ml) was stirred at room temperature with 6% w/v aqueous sodium dichromate (60 ml) for 15h. The reaction mixture was diluted with water to yield starting material (0.6g), identical (m.p. and i.r. spectrum) with an authentic sample. The aqueous filtrate was evaporated under reduced pressure and the residue was treated with a little water to yield a green intractable solid (0.1g). Extraction of the aqueous filtrate with chloroform gave no further material.

(ii) A boiling solution of 2-acetyl-3-hydroxyquinoline (311) (0.7g, 0.004 mol) in glacial acetic acid (20.0 ml), water (12.0 ml) and concentrated sulphuric acid (5.0 ml) was treated with a solution of sodium dichromate (6.0g) in water (15.0 ml) and the mixture was heated under reflux for 1h. The cooled reaction mixture was concentrated under reduced pressure and the residue was diluted with water and neutralised with 10% w/v aqueous sodium hydroxide giving a green intractable solid (0.5g). Extraction of the aqueous filtrate with chloroform gave no further material.

(c) Using Potassium Permanganate

(i) 2-Acetyl-3-hydroxyquinoline (311) (1.9g, 0.01 mol) in aqueous 1M-sodium hydroxide (120 ml) was heated under reflux

with potassium permanganate (1.8g). The colour of the solution was immediately discharged and further portions (1.8g) of potassium permanganate were added a little at a time until the purple colour persisted (total 14.4g). A little ethanol was added to reduce the excess of potassium permanganate. The manganese dioxide was filtered off and the aqueous alkaline filtrate was acidified with dilute aqueous hydrochloric acid. Carbon dioxide was evolved and the acidic solution was extracted with chloroform to give a red solid (0.1g). This solid dissolved in saturated aqueous sodium hydrogen carbonate with the evolution of carbon dioxide and was recovered unchanged on acidification. Recrystallisation gave orange crystals of azobenzene-2,2'-dicarboxylic acid (306), m.p. 240° (from ethanol) (lit.,[137] 245°), $\nu_{max.}$ 2750, 2550 (OH) and 1760 (CO) cm^{-1}, M^+ 270 (M 270).

(ii) 2-Acetyl-3-hydroxyquinoline (311) (0.6g, 0.003 mol) in 10% w/v aqueous sodium hydroxide (30.0 ml) was stirred at room temperature with potassium permanganate (0.5g). Further portions (0.5g) of potassium permanganate were added until the purple colour persisted. A total of 3.0g of potassium permanganate was required. Ethanol (2.0 ml) was added to reduce the excess of potassium permanganate. The manganese dioxide was filtered off and the aqueous alkaline filtrate was acidified with dilute aqueous hydrochloric acid and was extracted with chloroform. Evaporation of the extract gave a brown solid (0.2g) [$\nu_{max.}$ 3500, 3400 (NH_2), 2650br (OH) and 1680 (CO) cm^{-1}], sublimation of which gave a pure sample of anthranilic acid, m.p. 144°, identical (m.p. and i.r. spectrum) with an authentic sample.

(d) Using Hydrogen Peroxide

(i) 2-Acetyl-3-hydroxyquinoline (311) (0.4g, 0.002 mol) dissolved in 10% w/v aqueous sodium hydroxide (2.0 ml) was stirred at room temperature with 3% aqueous hydrogen peroxide (3.0 ml) for 15h. Acidification of the solution with dilute aqueous hydrochloric acid precipitated starting material (0.3g), identical (m.p. and i.r. spectrum) with an authentic sample. Extraction of the aqueous mother liquors with chloroform gave no further material.

(ii) 2-Acetyl-3-hydroxyquinoline (311) (0.4g, 0.002 mol) dissolved in glacial acetic acid (14 ml) was stirred at 50° with 30% aqueous hydrogen peroxide (5.0 ml, 0.008 mol) for 15h. The cooled reaction mixture was diluted with water (20 ml) and was filtered to give starting material (0.2g), identical (m.p. and i.r. spectrum) with an authentic sample. The aqueous filtrate was extracted with chloroform to give a red gum, which was triturated with ether to yield a light brown solid (0.2 g) whose t.l.c. in ether over silica indicated a mixture of two components. Treatment of the mixture with saturated aqueous sodium hydrogen carbonate gave a light coloured solid (0.07g) which was crystallised to afford 3-acetoxyquinolin-2(1H)-one (315), m.p. 212° (from ethanol), identical (m.p. and i.r. spectrum) with a sample prepared as described later. The sodium hydrogen carbonate filtrate was acidified with dilute aqueous hydrochloric acid to give a light coloured solid (0.02g), m.p. 154° (decomp.), $\nu_{max.}$ 3500-3200br, 2700br (OH) and 1720 (CO) cm^{-1}, M^+ 205, which was not characterised.

(e) Using 3-Chloroperbenzoic acid

A solution of 2-acetyl-3-hydroxyquinoline (311) (0.5g, 0.0025 mol) in chloroform (4.0 ml) was treated with a solution of 3-chloroperbenzoic acid (0.4g, 0.004 mol) in chloroform (4.0 ml) and the mixture was heated under reflux for 48h. The reaction mixture was cooled, washed with saturated aqueous sodium hydrogen carbonate and evaporated to give a yellow solid (0.4g) whose t.l.c. in ether over silica showed the presence of some starting material. Leaching of the mixture with a little ether removed the starting material leaving an insoluble solid which was crystallised to give 3-acetoxyquinolin-2(1H)-one (315), m.p. 211° (from ethanol), identified by comparison (m.p. and i.r. spectrum) with an authentic sample prepared as described later.

The Alkaline Hydrolysis of 3-Acetoxyquinolin-2(1H)-one (315)

3-Acetoxyquinolin-2(1H)-one (315) (0.07g) was treated with 10% w/v aqueous sodium hydroxide (ca. 1 ml). The salt which separated was collected and acidified with dilute aqueous hydrochloric acid to give 3-hydroxyquinolin-2(1H)-one (316) (0.03g), m.p. 251° (subl.), identical (m.p. and i.r. spectrum) with a sample prepared as described later.

Diazomethane was prepared as a solution in ether as described by De Boer and Backer.[138]

3-Hydroxyquinolin-2(1H)-one (316) was prepared[113] by reacting diazomethane with isatin (317) (27%), m.p. 254° (subl.) (from aqueous acetic acid) (lit.,[113] 258°).

3-Acetoxyquinolin-2(1H)-one (315) was prepared[113,114] by heating 3-hydroxyquinolin-2(1H)-one (316) (0.1g) under reflux

with acetic anhydride (ca. 1 ml) for 1h. The reaction mixture was allowed to cool and the solid which separated was collected and crystallised to afford the acetoxyquinolinone (315) (95%), m.p. 212° (from ethanol) (lit.,[113] 215°).

2-Acetyl-3-hydroxyquinoline Hydrazone (342)

2-Acetyl-3-hydroxyquinoline (311) (0.4g, 0.002 mol) dissolved in ethanol (7.0 ml) was heated under reflux with hydrazine monohydrate (0.1 ml, 0.002 mol) for 3h. The hydrazone (342) separated from the cooled solution and was collected and crystallised to give yellow needles (0.3g, 77%), m.p. 168° (subl.) (from ethanol), $\nu_{max.}$ 3400 and 3300 (NH_2) cm^{-1},

Found:	C,65.3;	H,5.6;	N,20.6%;	M^+ 201.
$C_{11}H_{11}N_3O$ requires:	C,65.7;	H,5.5;	N,20.9%;	M 201.

The Attempted Reaction of 2-Acetyl-3-hydroxyquinoline (311) with Alkali

2-Acetyl-3-hydroxyquinoline (311) (0.2g, 0.001 mol) in trigol (1.0 ml) was heated under reflux with potassium hydroxide (0.2g, 0.003 mol) for 2 min. The cooled mixture was diluted with water (3 ml) and was acidified with dilute aqueous hydrochloric acid. A dark green solid (0.1g) was collected and identified (i.r. spectrum) as starting material. Repetition of the reaction by heating under reflux for 10 min and the mixture worked-up as before gave an intractable gum from which no solid could be obtained.

The Reaction of 2-Acetyl-3-hydroxyquinoline (311) with Benzoic Anhydride

2-Acetyl-3-hydroxyquinoline (311) (0.7g, 0.004 mol) and benzoic anhydride (0.45g, 0.002 mol) in triethylamine (4.0 ml) were heated under reflux for 3h. The cooled reaction mixture was treated with ether and dilute aqueous hydrochloric acid. The ether phase was washed with saturated aqueous sodium hydrogen carbonate to remove any benzoic acid and was evaporated to give a yellow solid (0.5g) whose i.r. spectrum [$\nu_{max.}$ 1730, 1700 and 1650 (CO) cm^{-1}] suggested the presence of starting material. The solid was treated with chloroform (10.0 ml) and 10% w/v aqueous sodium hydroxide (5.0 ml). The aqueous alkaline phase gave, on acidification, starting material (0.2g) identical (m.p. and i.r. spectrum) with an authentic sample. The chloroform phase gave a sand coloured solid which was crystallised to afford 2-acetyl-3-benzoyloxyquinoline (341) (0.2g, 18%), m.p. 77° (from light petroleum), $\nu_{max.}$ 1730 and 1700 (CO) cm^{-1},

Found: C,74.2; H,4.5; N,4.8%; M^+ 291.

$C_{18}H_{13}NO_3$ requires: C,74.2; H,4.5; N,4.8%; M 291.

The Methylation of 2-Acetyl-3-hydroxyquinoline (311)

(a) 2-Acetyl-3-hydroxyquinoline (311) (0.7g, 0.004 mol) in acetone (100 ml) was heated under reflux with anhydrous potassium carbonate (4.2g) and dimethyl sulphate (2.4ml) for 4h. The insoluble potassium carbonate was filtered off and the acetone and dimethyl sulphate were evaporated under reduced pressure to give a gummy solid (0.7g). Trituration with ether and filtration gave a light coloured solid (0.1g)

which was crystallised to yield 2-acetyl-3-methoxy-1-methylquinolinium methosulphate (326), m.p. 182° (from ethanol-light petroleum), $\nu_{max.}$ 1720 (CO) cm^{-1}, τ [D_2O] 0.90-1.82 (5H,m,ArH), 5.18 (3H,s,Me), 5.46 (3H,s,Me), 5.92 (3H,s,Me) and 6.74 (3H,s,Me),

Found: C,51.4; H,5.2; N,4.4%; M^+ 216.

$C_{11}H_{17}NO_6S$ requires: C,51.4; H,5.2; N,4.3%; M(cation)216.

The ethereal filtrate was evaporated to give a gummy solid which on crystallisation afforded 2-acetyl-3-methoxyquinoline (327) (0.5g), m.p. 54° (from light petroleum, b.p. 40-60°), $\nu_{max.}$ 1690 (CO) cm^{-1}, τ [$CDCl_3$] 1.88-2.50 (5H,m,ArH), 6.03 (3H,s,Me) and 7.24 (3H,s,Me),

Found: C,71.4; H,5.5; N,6.8%; M^+ 201.

$C_{12}H_{11}NO_2$ requires: C,71.6; H,5.5; N,7.0%; M 201.

(b) The foregoing experiment was repeated on a ten-fold scale. The potassium carbonate was filtered off, the filtrate was evaporated under reduced pressure and the residual oil was left in contact with water for 1h. Extraction of the aqueous phase with chloroform yielded, as the sole product, 2-acetyl-3-methoxy-1-methylquinolinium methosulphate (326) (10.8g, 81%), identical (m.p. and i.r. spectrum) with a sample prepared previously.

The Reaction of 2-Acetyl-3-methoxy-1-methylquinolinium Methosulphate (326) with Alkali

The N-methylquinolinium methosulphate (326) (9g, 0.03 mol) was triturated with 10% w/v aqueous sodium hydroxide (50 ml) and the resultant gum was extracted with chloroform to give a very viscous gum (6.8g, 94%), identified as 1-methoxy-

2-(2-methylaminophenyl)-1-pyruvoylethylene (330), $\nu_{max.}$ 3500 (NH), 1720 and 1660 (CO) cm^{-1}, τ [$CDCl_3$] 2.50-3.52 (4H,m,ArH), 4.02 (1H,s,CH), 5.00 (1H,br,NH), 6.31 (3H,s,OMe), 7.26 (3H,s,NMe) and 7.72 (3H,s,COMe), M^+ 233 (M 233).

The Reaction of 1-Methoxy-2-(2-methylaminophenyl)-1-pyruvoylethylene (330) with ortho-Phenylenediamine

The dicarbonyl compound (330) (6.5g, 0.03 mol) dissolved in ethanol (30 ml) was heated under reflux with ortho-phenylenediamine (3.2g, 0.03 mol) for 0.5h. The cooled reaction mixture was filtered to give the quinoxaline derivative (334) which was combined with a second crop (total 3.6g, 39%) obtained by evaporating the ethanol filtrate and triturating the residue with ether. The quinoxaline derivative (334) crystallised as yellow needles, m.p. 178° (from ethanol), $\nu_{max.}$ 3400 (NH) and 1640 (C=C) cm^{-1}, τ [$CDCl_3$] 1.92-3.80 (m,ArH), 4.08 (s,CH), 4.26 (s,CH), 6.10 (s,Me), 6.36 (s,Me), 7.20 (s,Me), 7.27 (s,Me), 7.48 (s,Me) and 7.80 (s,Me),

Found: C,74.9; H,6.4; N,13.6; M^+ 305.

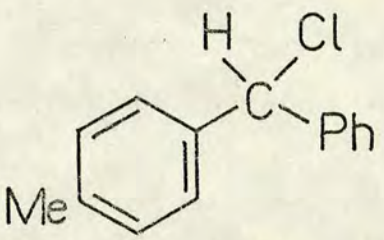
$C_{19}H_{19}N_3O$ requires: C,74.7; H,6.2; N,13.8; M 305.

Chapter Three

Studies on the Synthesis and Reactivity of Substituted 2-Nitrophenylethylene Oxides

3.1. Introduction

Generally, para-substituted benzhydryl halides are solvolysed faster than the corresponding ortho-substituted isomers.[139] For example the solvolysis of para-methylbenzhydryl chloride (350) in ethanol occurs six times faster than



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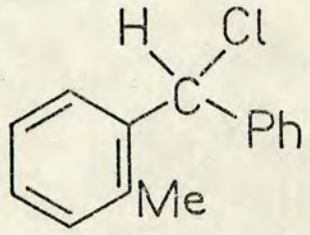
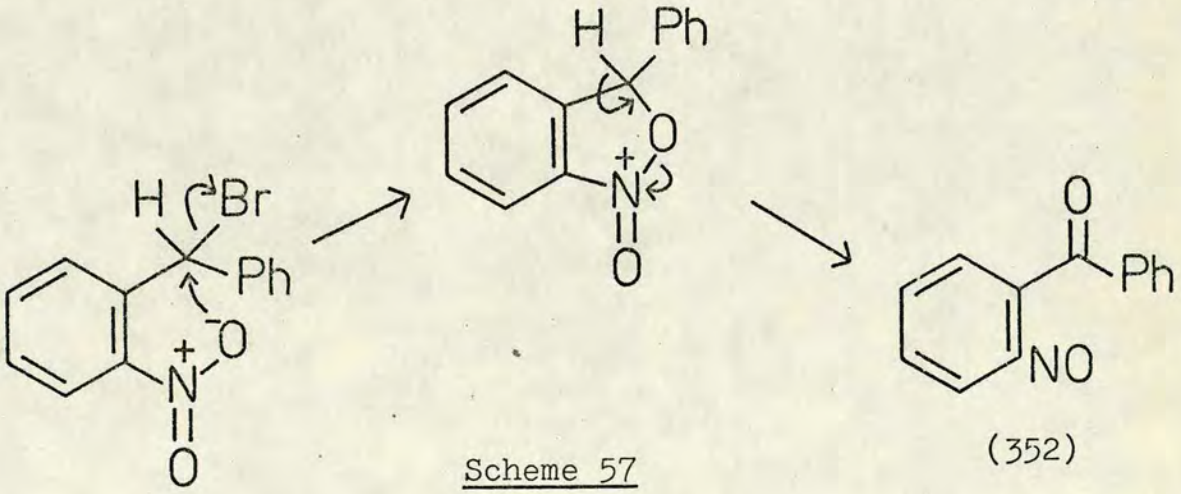


(351)

the solvolysis of the ortho-methylbenzhydryl chloride (351). However in acetic acid at 45° the acetolysis rate ratio of ortho and para-nitrobenzhydryl bromide is 1450:1,[140] the product from the ortho-isomer being ortho-nitrosobenzophenone (352). The faster rate of acetolysis for ortho-nitrobenzhydryl

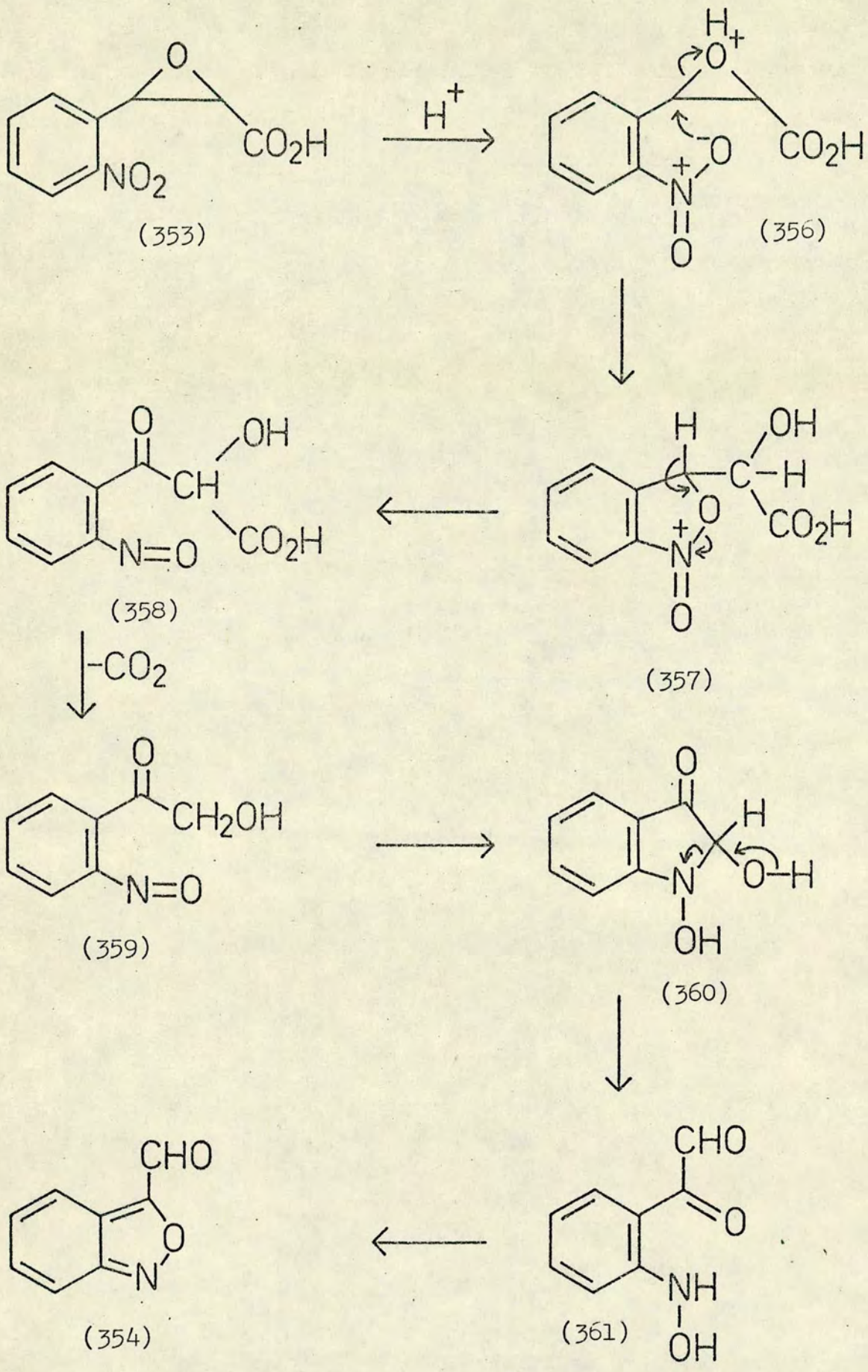


Scheme 57

(352)

bromide is interpreted (Scheme 57) as illustrating the capability of the ortho-nitro-group to function as an internal nucleophile and thus to anchimerically assist displacement of bromide ion.

Participation by the nitro-group is also proposed to account for the formation of 6-chloro-1-hydroxyquinolinones (119)

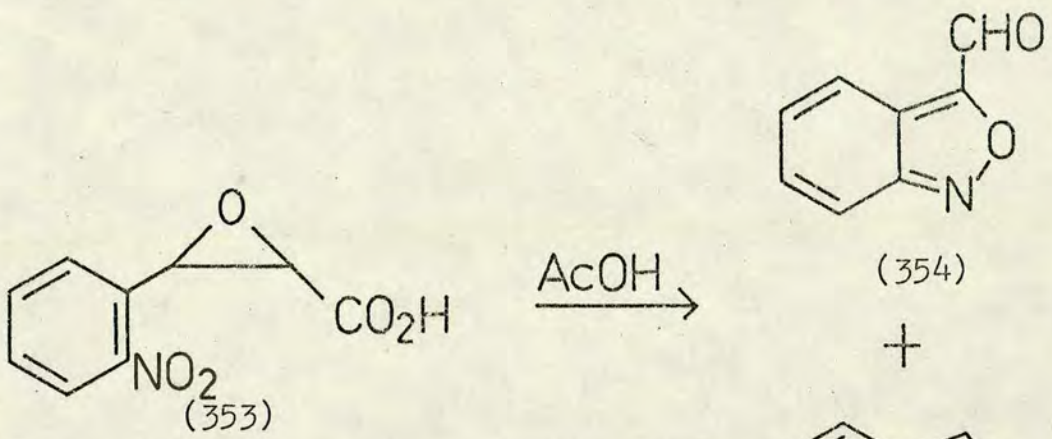


(353) (356) (358) (357) (359) (360) (354) (361)

Scheme 58

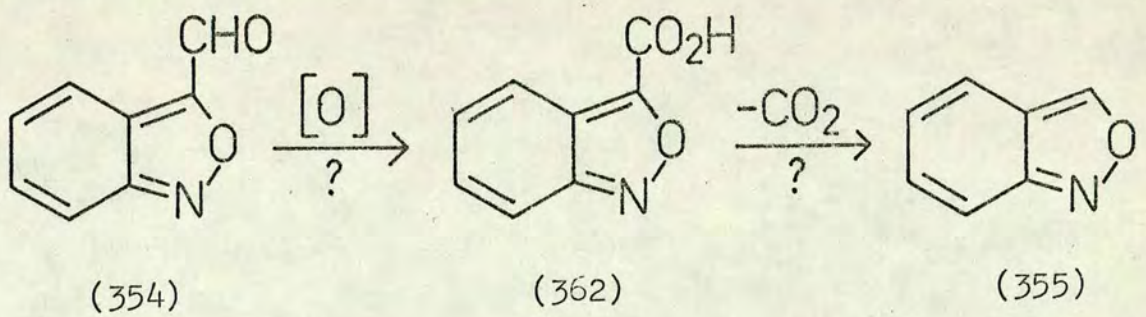
in the condensation of 2-nitrobenzaldehyde (117) with active methylene compounds (118) (cf. Scheme 21 and page 24).

Examples are also known of the intramolecular interaction between an aromatic nitro-group and an epoxide ring. When 2-nitrophenylglycidic acid (353) is heated with glacial acetic



(353) (354) + (355)

acid,[141] a mixture of anthranil-3-carboxaldehyde (354) and anthranil (355) is produced. The formation of the aldehyde (354) can be explained (Scheme 58) by intramolecular nucleophilic attack by the nitro-group on the protonated epoxide ring and subsequent oxygen transfer [(356)→(357)→(358)] to afford the nitroso-intermediate (358). The oxygen transfer process is a common feature of the acid-catalysed reactions of ortho-nitrobenzene derivatives (see page 22). Decarboxylation of (358) and internal oxidation-reduction in (359) yields [(359)→(360)→(361)] the hydroxylaminoketone (361), cyclisation of which gives anthranil-3-carboxyaldehyde (354). Oxidation[141] of the aldehyde (354) to anthroxanic acid (362) and decarboxylation[142] of the acid (362) to anthranil (355) then explain the

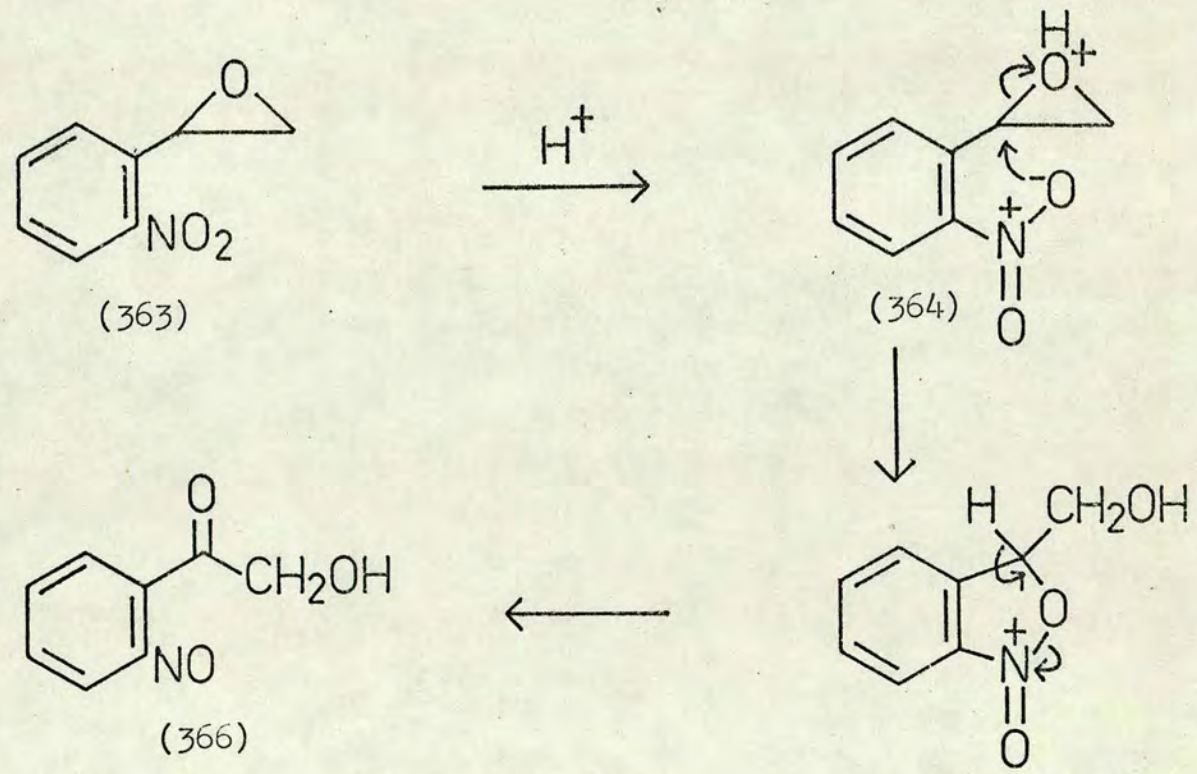


(354) (362) (355)

Scheme 59

concurrent formation of anthranil (355; Scheme 59).

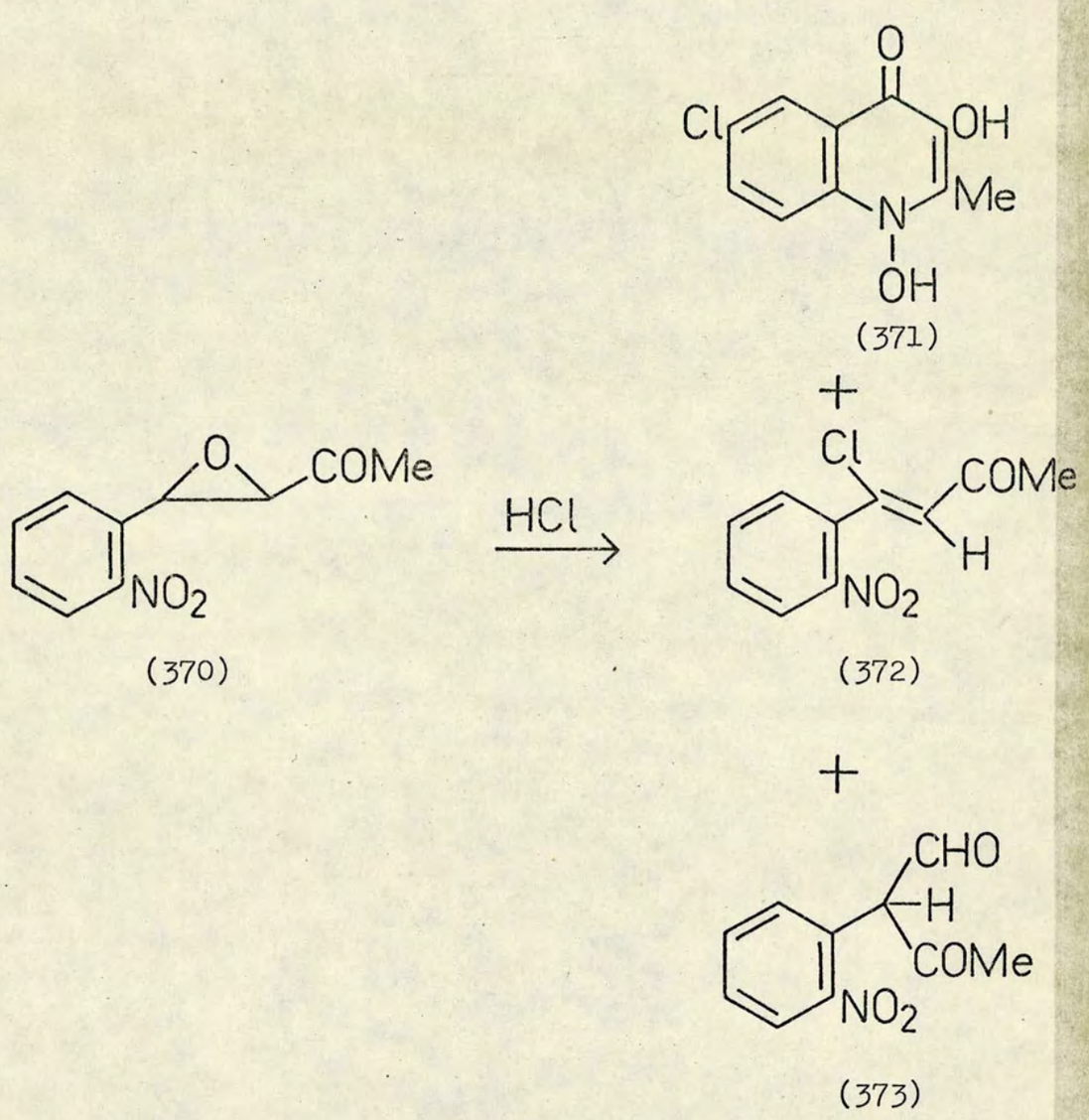
A related reaction to that of 2-nitrophenylglycidic acid (Scheme 58) is the formation[143,144] of 2-nitrosobenzoylmethanol (366) by reaction of 2-nitrophenylethylene oxide (363)



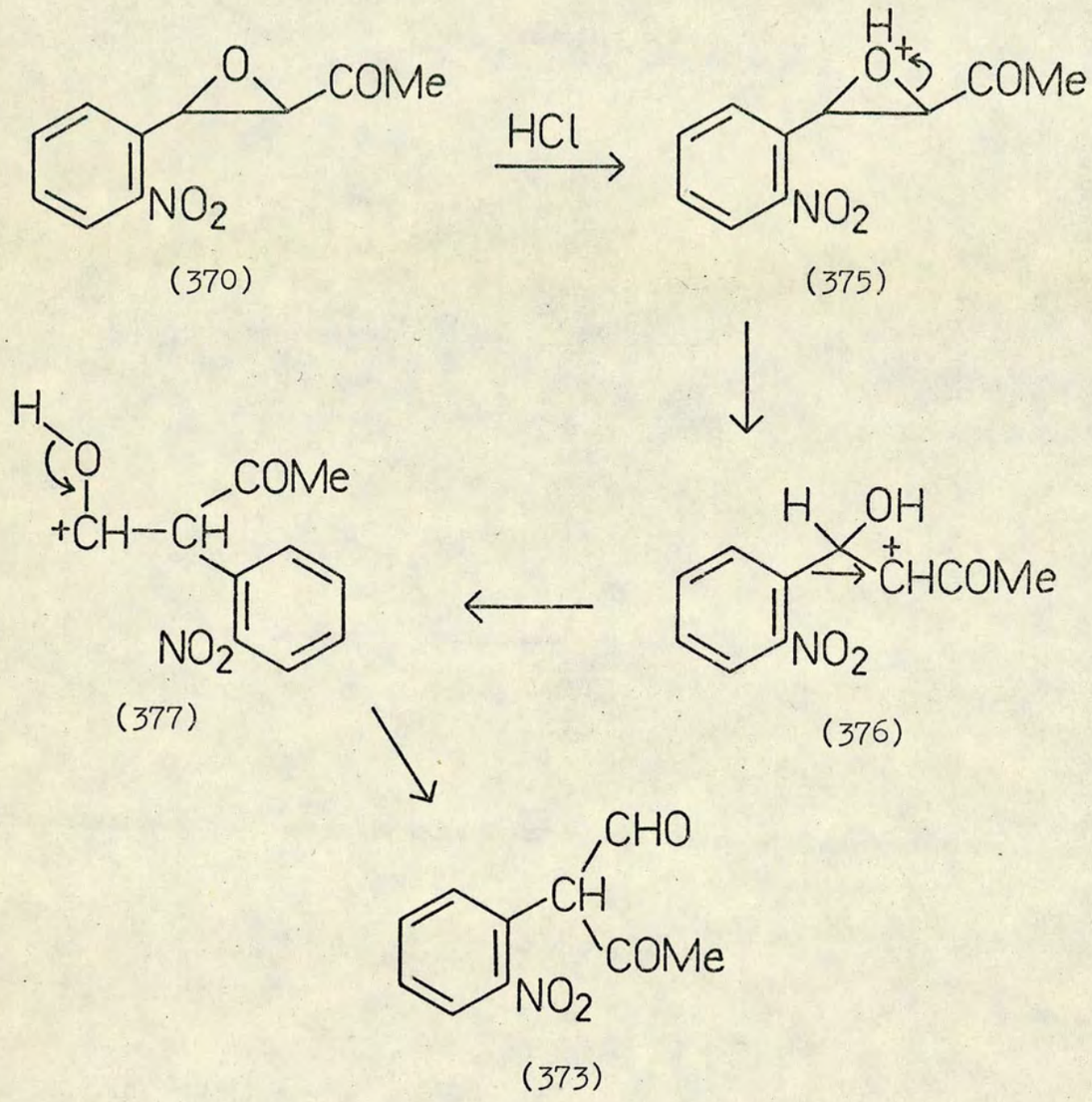
(363) (364) (365) (366)

Scheme 60

with formic acid. This reaction (Scheme 60) can be depicted as involving nucleophilic attack by oxygen on the epoxide ring [(364)→(365)] and subsequent decomposition of the cyclic intermediate [(365)→(366)] with oxygen transfer, by analogy with the mechanism proposed for the solvolysis of



(370) (372) (371) (373)

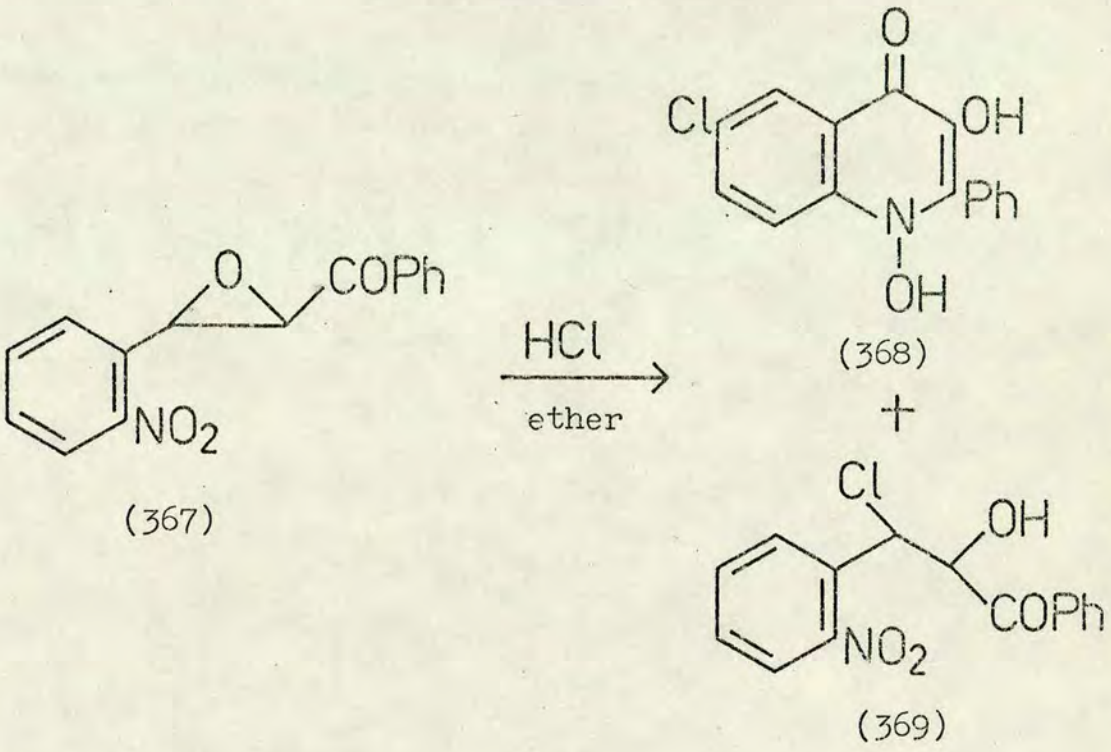


(370) (375) (377) (376) (373)

Scheme 61

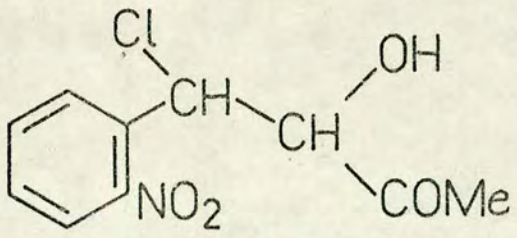
2-nitrobenzhydryl bromide (Scheme 57).

More recently[145,146] the reaction of trans-1-benzoyl-2-(2-nitrophenyl)ethylene oxide (367) with ethereal hydrogen



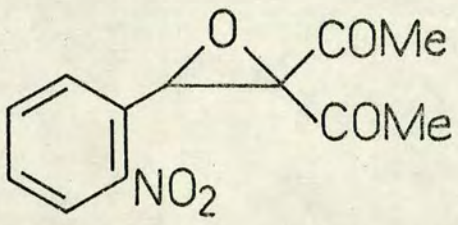
(367) (368) (369)

chloride has been shown to give the 6-chloroquinolinone (368) in low yield together with the chlorohydrin (369) which is the major product. The reaction[145] of trans-1-acetyl-2-(2-nitrophenyl)ethylene oxide (370) under the same conditions gave a low yield of the corresponding chloroquinolinone (371) together with the benzylidene derivative (372) and the keto-aldehyde (373). The product (372) presumably results from dehydration of the corresponding chlorohydrin (374) while formation of (373) is explicable in terms of the well known[147] acid-catalysed rearrangement of epoxides. Ring-opening of the protonated epoxide [(375); Scheme 61] to the carbonium ion (376), migration of the ortho-nitrophenyl group and loss of a proton [(376)→(377)→(373)] thus account for the formation of (373).

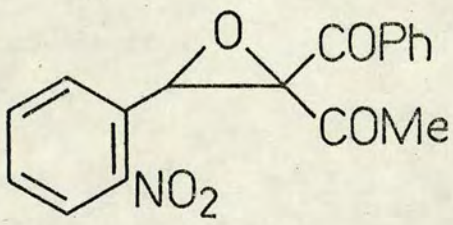


(374)

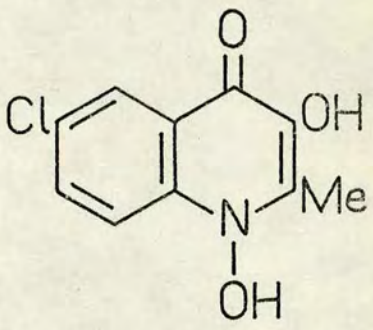
In contrast to the low yields of quinolinones from the epoxides (367) and (370), the dicarbonyl epoxides (378) and



(378)

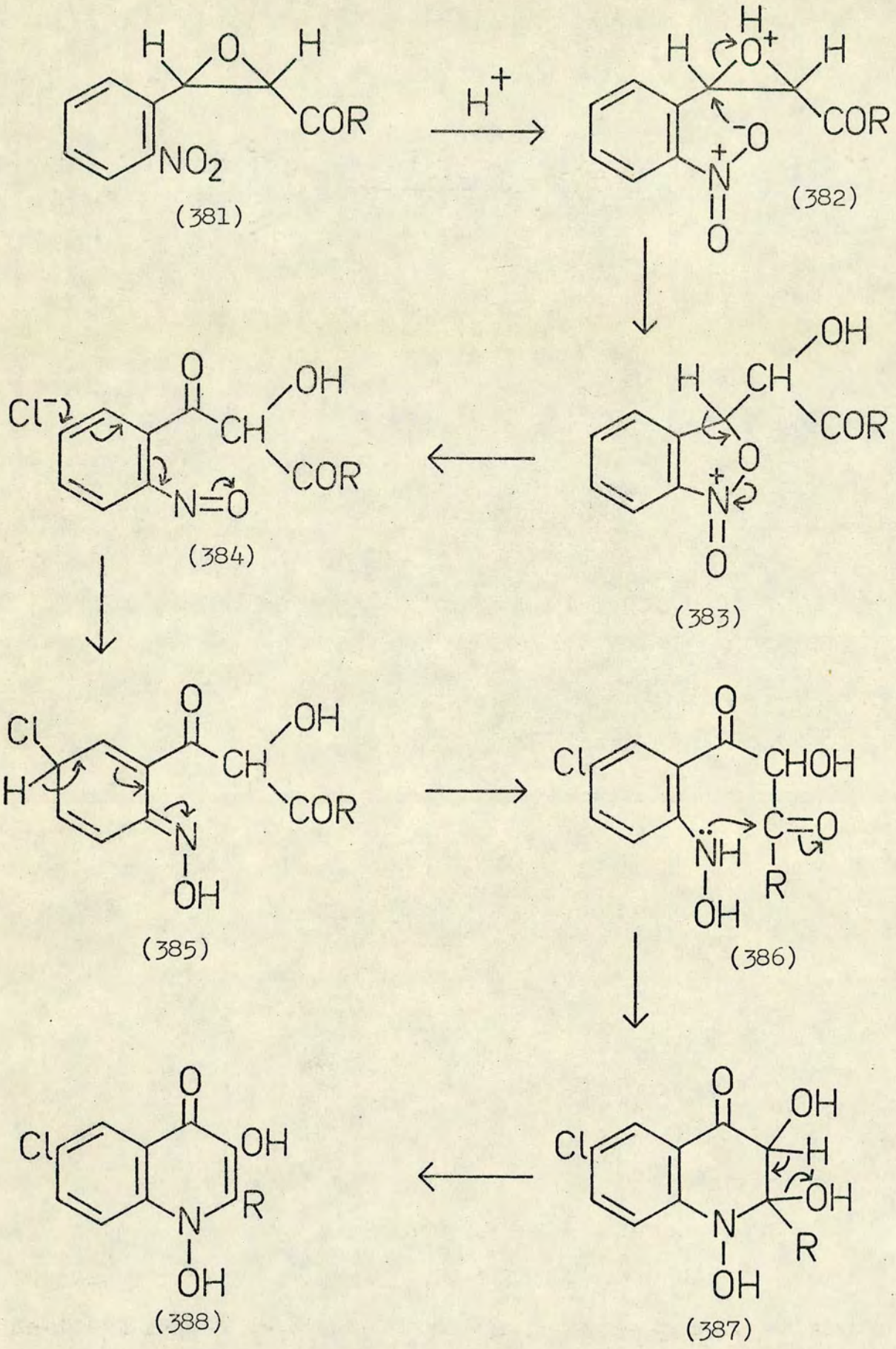


(379)

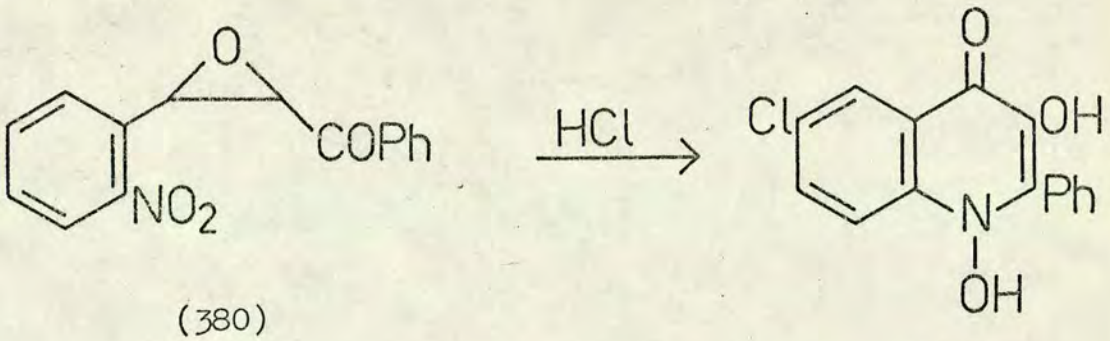


(371)

(379) are converted[145] into the chloroquinolinone (371) in excellent yield. The higher yields of cyclised products in the cases of the epoxides (378) and (379) are possibly associated with the presence of the cis-carbonyl function. Confirmation of this suggestion is provided[145] by the demonstration that cis-1-benzoyl-2-(2-nitrophenyl)ethylene oxide (380), unlike the trans-isomer is transformed in high yield (90%) into the chloroquinolinone (368).



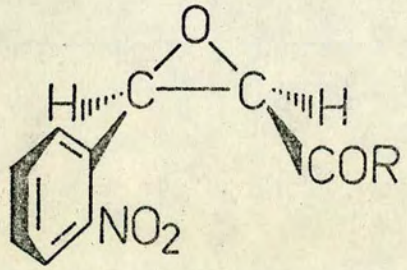
Scheme 62



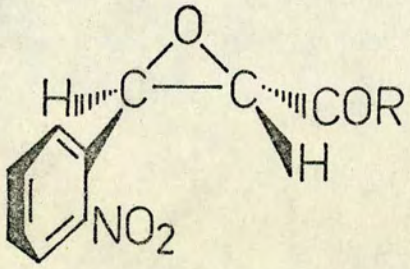
(380) (368)

The formation of chloroquinolinones (388) from acylated 2-nitrophenylethylene oxides (381) has been rationalised[145,146] by a course (Scheme 62) whose initial steps [(381)→(382)→(383)→(384)] are entirely analogous to those invoked (Scheme 58) to account for the formation of anthranil-3-carboxaldehyde (354) from 2-nitrophenylglycidic acid (353). Reduction of the nitroso-group in (384) to the hydroxylamine [(384)→(385)→(386)] occurs indirectly with the incorporation of chlorine (cf. page 24). However if the reaction is carried out in the presence of hydroquinone, the reduction step [(384)→(386)] is effected directly and a chlorine-free product (388, H for Cl) is obtained. The final cyclisation step is an example of the known[47] hydroxylamino-ketone condensation.

However it is not clear from this mechanism why diacyl epoxides and cis-monoacyl epoxides give high yields of 1-hydroxyquinolinones, whereas only low yields are obtained from trans-monoacyl epoxides. Thus, any potential advantage (in terms of ease of cyclisation) associated with the closer proximity of a cis-acyl group to the nitrogen centre involved in the cyclisation, will surely be lost once the epoxide ring



(389)



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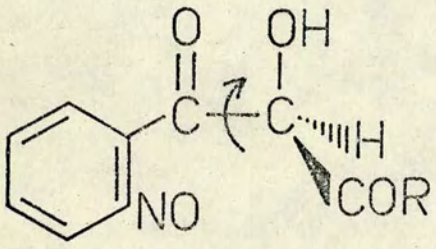
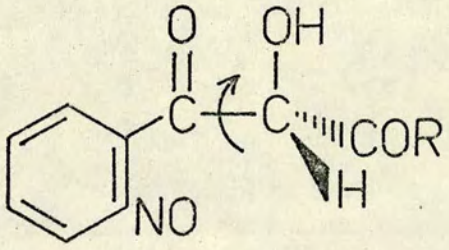


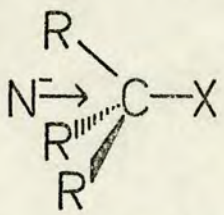
(391)



(392)

Scheme 63

is opened and the hydroxycarbonyl moiety [CH(OH)COR] produced is free to rotate. In other words both cis (389) and trans (390) epoxides (Scheme 63) give intermediates (391) and (392) which differ only in the arrangement of groups around the asymmetric carbon atom and, by rotation about the bonds indicated both structures can attain conformations favourable to ultimate cyclisation. The difference in the reactivity of the cis and trans-epoxides must thus reside in the intact epoxide structures (381) and (382) (Scheme 62). The fact that chlorohydrin formation is the major competing reaction in the case of the trans-epoxide (367), also indicates that the difference in reactivity must be associated with the early stages of epoxide ring-opening. One possible explanation is that the cis-acyl group exerts a buttressing effect on the 2-nitrophenyl substituent. For efficient ring-opening of the protonated epoxide ring (382), just as in a nucleophilic S_N2 displacement, the nucleophile, the carbon atom being attacked and the leaving

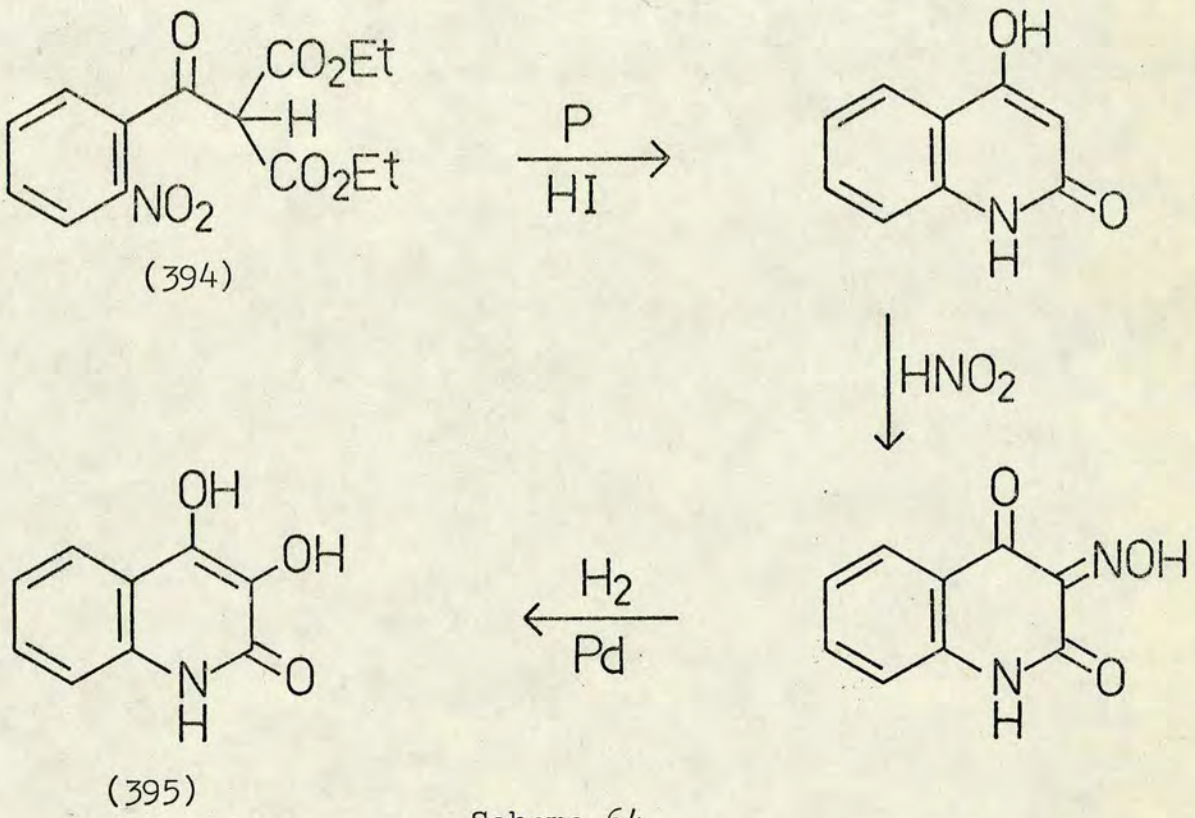


(393)

group must be collinear as in (393). Thus a cis-carbonyl group may exert a steric effect by forcing the nitrophenyl substituent to assume an orientation in which the nitro-group is held in a suitable position for nucleophilic attack. In this position the nitro-group will also block external attack by chloride ion and so inhibit chlorohydrin formation. In the trans-epoxide no constraint is placed on the nitrophenyl group

and so there is competition between chlorohydrin formation and acid-catalysed epoxide rearrangement on the one hand and participation by the nitro-group on the other.

Relatively few syntheses of 3-hydroxyquinolin-4(1H)-ones are known. 3,4-Dihydroxyquinolin-2(1H)-one (395) has been prepared[148] from diethyl 2-nitrobenzoylmalonate (394) by the method outlined in Scheme 64. Another route to 3-hydroxy-

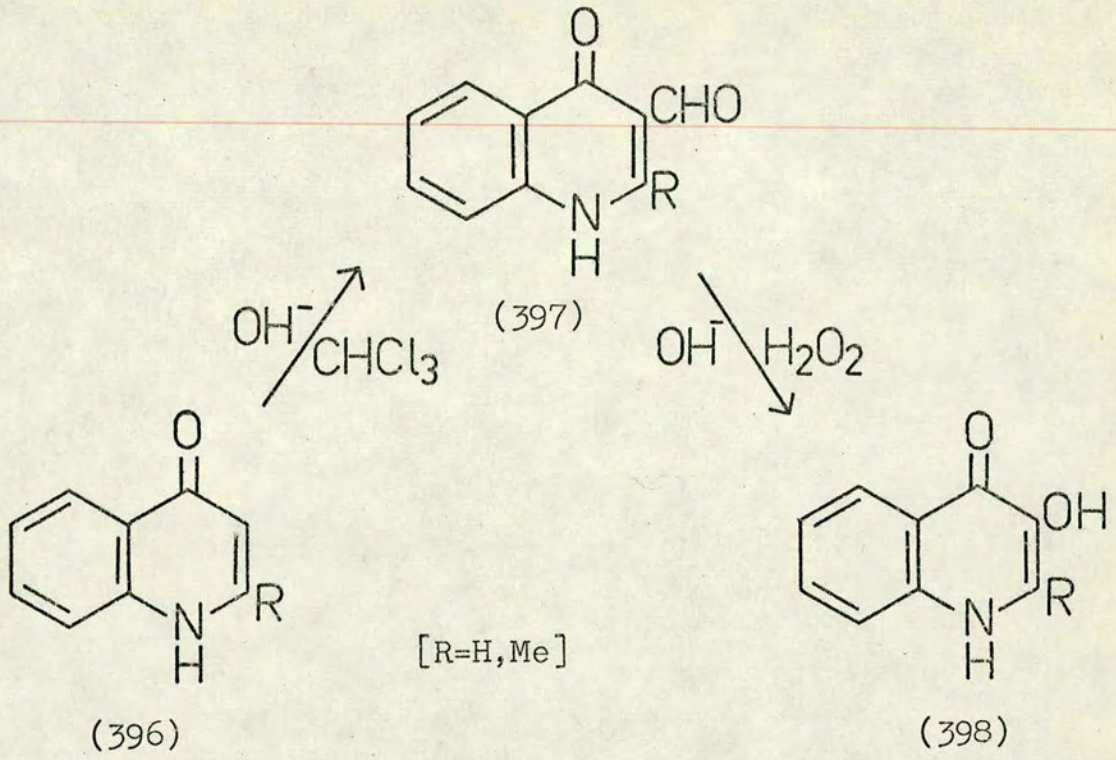


(394)

(395)

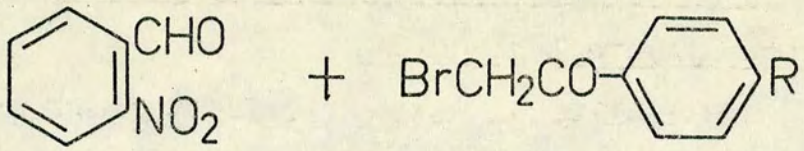
Scheme 64

quinolin-4(1H)-ones involves the Reimer-Tiemann reaction of a quinolin-4(1H)-one (396) to yield the corresponding aldehyde (397), Dakin oxidation of which affords the 3-hydroxyquinolin-4(1H)-one (398).[149] However in general 3-hydroxyquinolin-4(1H)-ones are relatively inaccessible compounds. It was therefore worthwhile to study the acid-catalysed reactions of acylated 2-nitrophenylethylene oxides in general, both from a

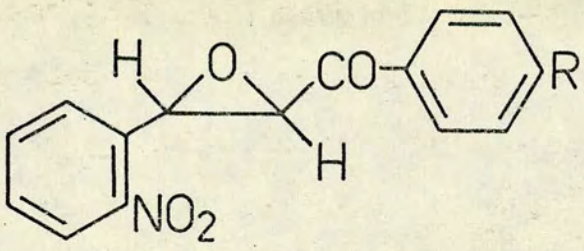


(396) (398)

synthetic viewpoint and in order to gain further information on mechanism.



(399)



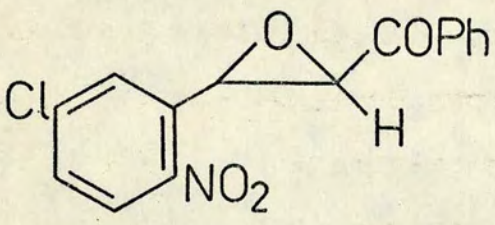
(400)

R

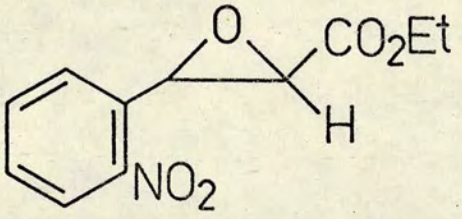
a; Br

b; Ph

c; NO_2



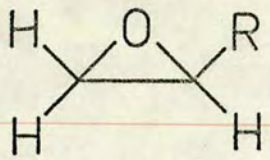
(401)



(402)

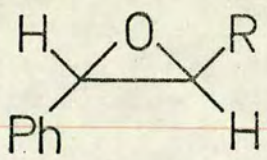
3.2. The Attempted Epimerisation of trans-1-Aroyl-2-(2-nitrophenyl)ethylene Oxides

Initially, an attempt was made to demonstrate further examples of the enhanced reactivity of cis-1-aroyl-2-(2-nitrophenyl)ethylene oxides (compared with the trans-isomers) in terms of acid-catalysed nitro-group participation with formation of 2-aryl-1,3-dihydroxyquinolin-4(1H)-ones. It was hoped to obtain the cis-epoxides required as substrates by the epimerisation of the corresponding trans-isomers (400a-c), (401) and (402). The latter were readily prepared in moderate to good yield (62-86%) by Darzens condensation of 2-nitrobenzaldehyde with para-substituted phenacyl bromides (399a-c), using a method based on that described by Cromwell and Setterquist.[150] Similar condensation of 5-chloro-2-nitrobenzaldehyde with phenacyl bromide (399, R=H) yielded the trans-5-chlorochalcone epoxide (401). The trans-2-nitrophenylglycidic ester (402) was likewise prepared by the sodium ethoxide catalysed condensation of 2-nitrobenzaldehyde with ethyl chloroacetate. It has been established[150,151] that the Darzens condensation gives the trans-epoxide rather than the cis-epoxide and on this basis the epoxides (400a-c),(401), and (402) are also assigned the trans-configuration. It has been shown[152,153,154] for a variety of epoxides (403), (404) and (405) that the trans-hydrogen coupling constants fall in the range 2.0 to 2.6 Hz whereas the cis-hydrogen coupling constants range from 4.0 to 4.9 Hz. The hydrogen coupling constants of 2 Hz shown by the Darzens condensation products (400a-c), (401) and (402) are thus in accord with the trans-configuration assigned to these compounds.



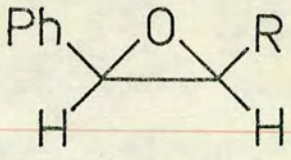
(403)

R = CHO, CH_2Cl, Me, CN, COMe, CO_2H, Ph



(404)

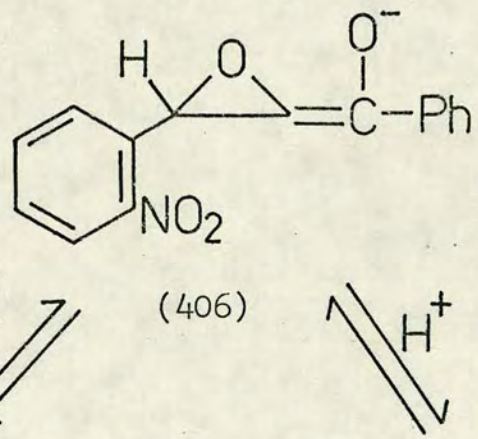
R = Me, Et, Pr^i, CN CO_2Et, OMe, OAc



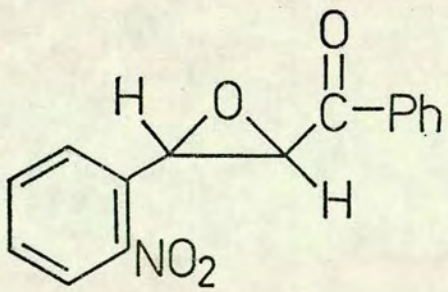
(405)

R = CN, OAc

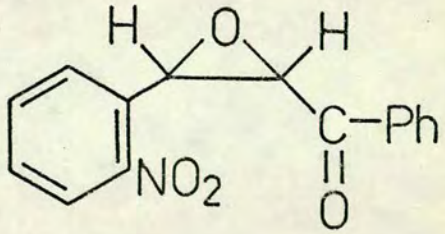
Cromwell and Setterquist[150] have epimerised trans-1-benzoyl-2-(2-nitrophenyl)ethylene oxide (367) to cis-1-benzoyl-2-(2-nitrophenyl)ethylene oxide (380) by treatment with methanolic sodium methoxide. The less soluble cis-isomer precipitates from the reaction mixture. Epimerisation (Scheme 65) proceeds via the enolate ion (406) which on protonation can either



(406)



(367)



(380)

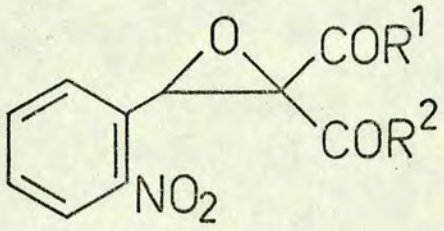
Scheme 65

revert to the trans-epimer or form the cis-epimer. It is claimed[150,155] that the trans-isomer is the kinetically controlled product which is slowly transformed into the thermodynamically more stable cis-isomer. However, application of these conditions of epimerisation to the trans-epoxides (400a-c), (401) and (402) was unsuccessful. Due to the insolubility of (400a) in methanol, epimerisation was attempted using dimethyl sulphoxide as solvent but again only unchanged trans-isomer was isolated. These results are not too surprising in view of the work by Kwart and Kirk[151] who argue that the trans-epoxide is the more thermodynamically stable isomer, there being large steric effects opposing the formation of cis-substituents on small rings. They rationalise the successful epimerisation of trans-1-benzoyl-2-(2-nitrophenyl)ethylene oxide (367) by Cromwell and Setterquist[150] as being due to precipitation of the cis-isomer from solution thus displacing the enolisation equilibrium (Scheme 65) to the right. The criterion therefore for successful epimerisation by equilibration through the enolate ion is that the cis-epimer should be more insoluble than the trans-epimer.

Although the cis-epimer is presumably the thermodynamically unstable isomer it was considered possible that it might be produced by acidification of the enolate ion under conditions of kinetic control. A solution of the trans-epoxide (400b) in dioxan was treated with sodium hydride causing complete transformation into the enolate ion. However acidification of the enolate ion using an excess of glacial acetic acid in ether gave only the unchanged trans-epoxide (400b) (90%).

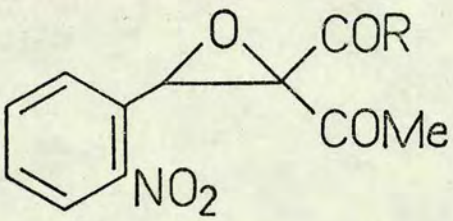
Since cis-1-aroyl-2-(2-nitrophenyl)ethylene oxides were

not readily accessible, attention was next directed to the study of the acid-catalysed reactivity of 1,1-diacylated 2-(2-nitrophenyl)ethylene oxides (407) and related substrates.



(407)

Initially, however, a suitable general method for the synthesis of epoxides of this type had to be developed. A previous study[145] has shown that the direct epoxidation of the 2-nitrobenzylidene derivatives of acetylacetone and benzoylacetone can give good yields of the corresponding diacyl-epoxides (408a and b) but the yields of these reactions tend to be irreproducible.



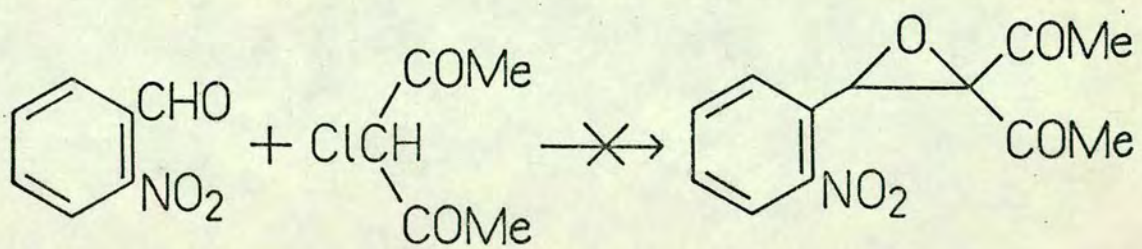
R

a; Me

b; Ph

(408)

As discussed before, the Darzens condensation provides a suitable general route to 1-aroyl-2-(2-nitrophenyl)ethylene

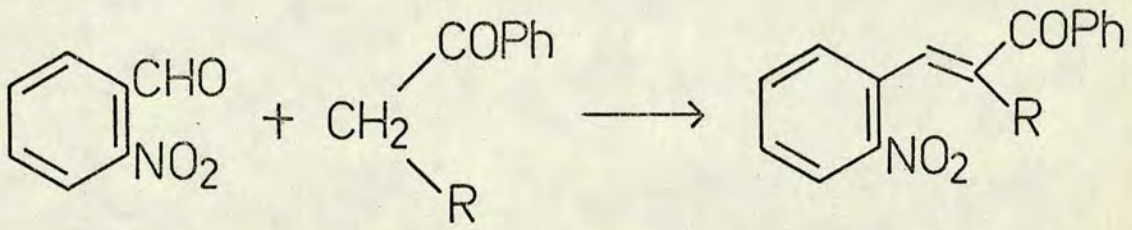


(409) (408a)

oxides. However attempts to apply this method to the diacyl-epoxides were unsuccessful. Thus, the attempted condensation of 2-nitrobenzaldehyde with 3-chloropentane-2,4-dione (409) in the presence of sodium carbonate failed to give any identifiable products.

3.3. The Preparation of the 2-Nitrobenzylidene Derivatives of Active Methylene Compounds

In view of the failure of the Darzens condensation it was decided to reinvestigate the direct epoxidation of readily available 2-nitrobenzylidene derivatives as a means of obtaining the required epoxides. The 2-nitrobenzylidene compounds required for study were readily prepared by the condensation of 2-nitrobenzaldehyde with active methylene



(410) (411)

	a	b	c	d	e	f	g
R;	H	CO_2Et	COMe	CN	COPh	Ph	Me

compounds under acidic and basic conditions. 2-Nitrobenzylideneacetophenone (411a) was available[156] by the sodium hydroxide catalysed reaction of 2-nitrobenzaldehyde with acetophenone (410a) while the hydrogen chloride catalysed condensation[157] of the aldehyde with deoxybenzoin (410f) afforded the phenyl analogue (411f). The similar condensation[5] of 2-nitrobenzaldehyde with propiophenone (410g) in the presence of hydrogen chloride gave a low yield of 2-nitrobenzylidenepropiophenone (411g), whose ^1H n.m.r. spectrum indicated it to be a mixture of the two possible geometrical isomers. 2-Nitrobenzylidenedibenzoylmethane (411e) was prepared by the piperidine catalysed condensation of 2-nitrobenzaldehyde with dibenzoylmethane (410e) as described by

Sword[5] with the modification that only a slight excess of dibenzoylmethane was used. Under the same conditions ethyl benzoylacetate (410b) gave an excellent yield of ethyl 2-nitrobenzylidenebenzoylacetate (411b), whereas benzoylacetone (410c) gave only a low yield of the product (411c). Piperidine also catalysed the condensation between 2-nitrobenzaldehyde and benzoylacetonitrile (410d) to give, albeit in low yield, the benzylidene derivative (411d) whose elemental analysis and spectral properties were fully in accord with the assigned structure.

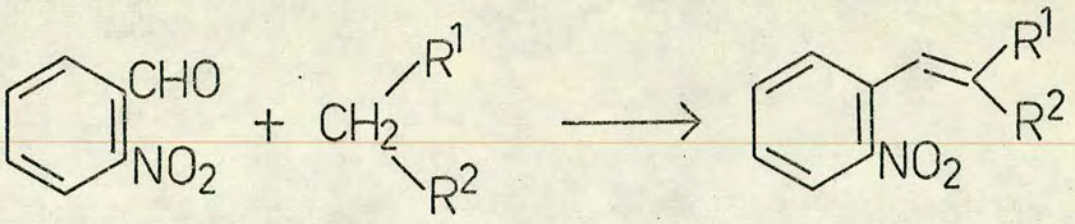
In the piperidine catalysed condensation of 2-nitrobenzaldehyde with ethyl acetoacetate (412b), ethyl 2-nitro-

(412) (413)

R; a CO_2Et b COMe c CN

benzylideneacetoacetate (413b) was obtained as an oil whose ^1H n.m.r. spectrum was consistent with the presence of the two possible geometrical isomers. Diethyl 2-nitrobenzylidenemalonate (413a) was prepared as described by Loudon and Wellings[4] but it was necessary to remove contaminating benzaldehyde from the product by steam distillation. The sodium ethoxide catalysed condensation[158] of 2-nitrobenzaldehyde with ethyl cyanoacetate (412c) afforded (413c) in good yield.

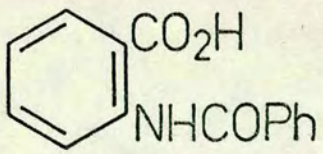
2-Nitrobenzylideneacetylacetone (415a) was prepared by



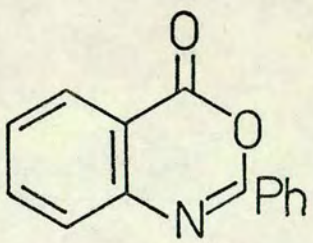
(414) (415)

	R^1	R^2
a;	COMe	COMe
b;	CN	Ph
c;	CN	$CONH_2$
d;	$CONH_2$	$CONH_2$
e;	CN	CN

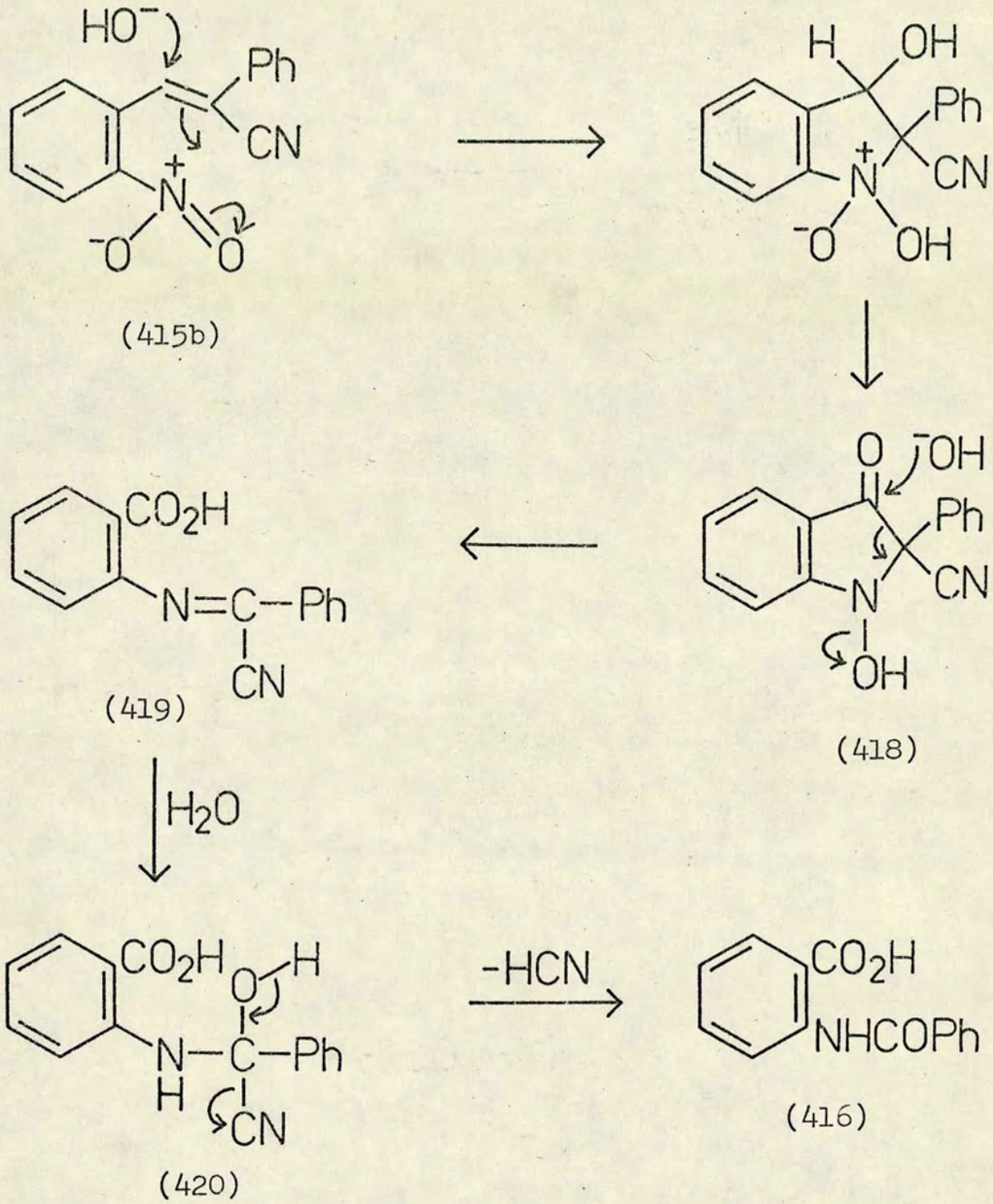
the method of Sword[5] but using only a slight excess of acetylacetone (414a). The benzylidene derivatives (415c) and (415e) were available in excellent yields by literature methods.[159] The sodium methoxide catalysed condensation[160] of 2-nitrobenzaldehyde with phenylacetonitrile (414b) gave a moderate yield of 2-nitrobenzylidenephenylacetonitrile (415b). Also isolated in this reaction was a solid whose i.r. spectrum indicated that it was a mixture of 2-benzamidobenzoic acid (416) and its internal anhydride (417). Treatment



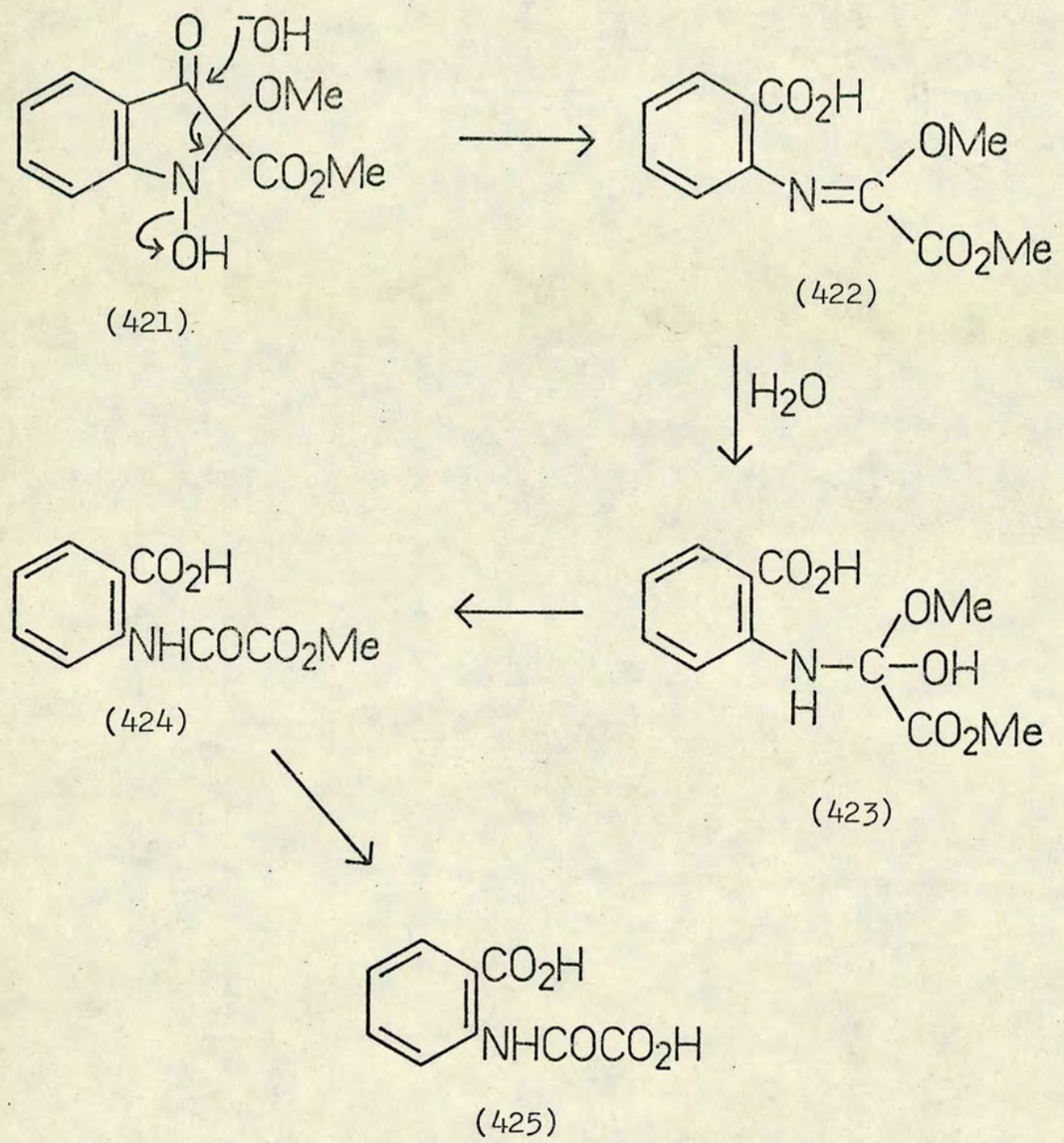
(416)



(417)



Scheme 66

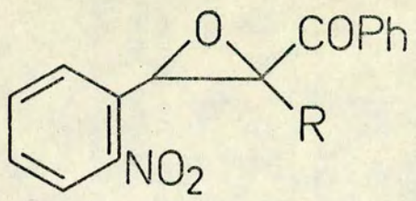


Scheme 67

of the mixture with aqueous sodium hydroxide hydrolysed the anhydride (417) and acidification afforded 2-benzamidobenzoic acid (416). The concurrent formation of the acid (416) in the preparation of the benzylidene derivative (415b) is rationalised in terms of the known[161] base-catalysed conversion of the latter into 2-benzamidobenzoic acid (416). A plausible mechanism (Scheme 66) involves attack by hydroxide ion on the benzylidene derivative (415b) causing cyclisation to the indolinone (418) which on further attack by hydroxide ion undergoes ring-opening to (419). Hydration of (419) gives the cyanohydrin (420) which by loss of hydrogen cyanide affords the acid (416). There is some analogy for this course in the known[162] base-catalysed conversion of the 1-hydroxyindolinone (421) (Scheme 67) into N-oxalylanthranilic acid (425). In this case hydration of the anil (422), formed by ring-opening of (421) yields a hemiketal (423) which reverts to the ketone (424). Hydrolysis of the ester function in (424) then accounts for the formation of N-oxalylanthranilic acid (425).

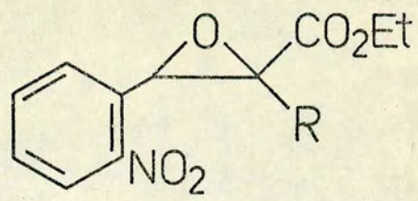
The attempted condensation of 2-nitrobenzaldehyde with malonamide (414d) catalysed by piperidine or by sodium ethoxide resulted only in the recovery (> 80%) of the aldehyde. However Zabicky[163] has prepared both meta and para-nitrobenzylidenemalonamide by shaking a suspension of the nitro-aldehyde and malonamide (414d) in aqueous ethanolic potassium hydroxide. When these conditions were applied to the synthesis of 2-nitrobenzylidenemalonamide (415d) a solid was isolated and shown by t.l.c. to be a single component. I.r. and mass spectral

data were consistent with the structure of the expected product (415d) although the mass spectrum indicated the presence of unreacted malonamide and the ^{1}H n.m.r. spectrum showed the presence of a little 2-nitrobenzaldehyde. The crude solid melted almost entirely in the range 40-43° (the m.p. of 2-nitrobenzaldehyde is 43-45°) but complete melting did not occur until 131-135° (the melting point of malonamide is 170°) and attempted crystallisation of the crude material resulted only in the isolation of malonamide. These results are reconcilable with the crude product being a mixture of both starting materials only. Despite its uncertain constitution however, the crude benzylidene derivative (415d) was used without further purification.



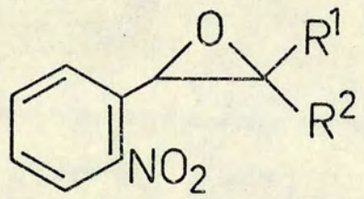
(428)

	R
a;	H
b;	CO_2Et
c;	COMe
d;	CN
e;	COPh
f;	Ph
g;	Me



(429)

	R
a;	CO_2Et
b;	COMe
c;	CN
d;	$CONH_2$



(430)

	R^1	R^2
a;	COMe	COMe
b;	CN	Ph
c;	CN	$CONH_2$
d;	$CONH_2$	$CONH_2$
e;	CN	CN

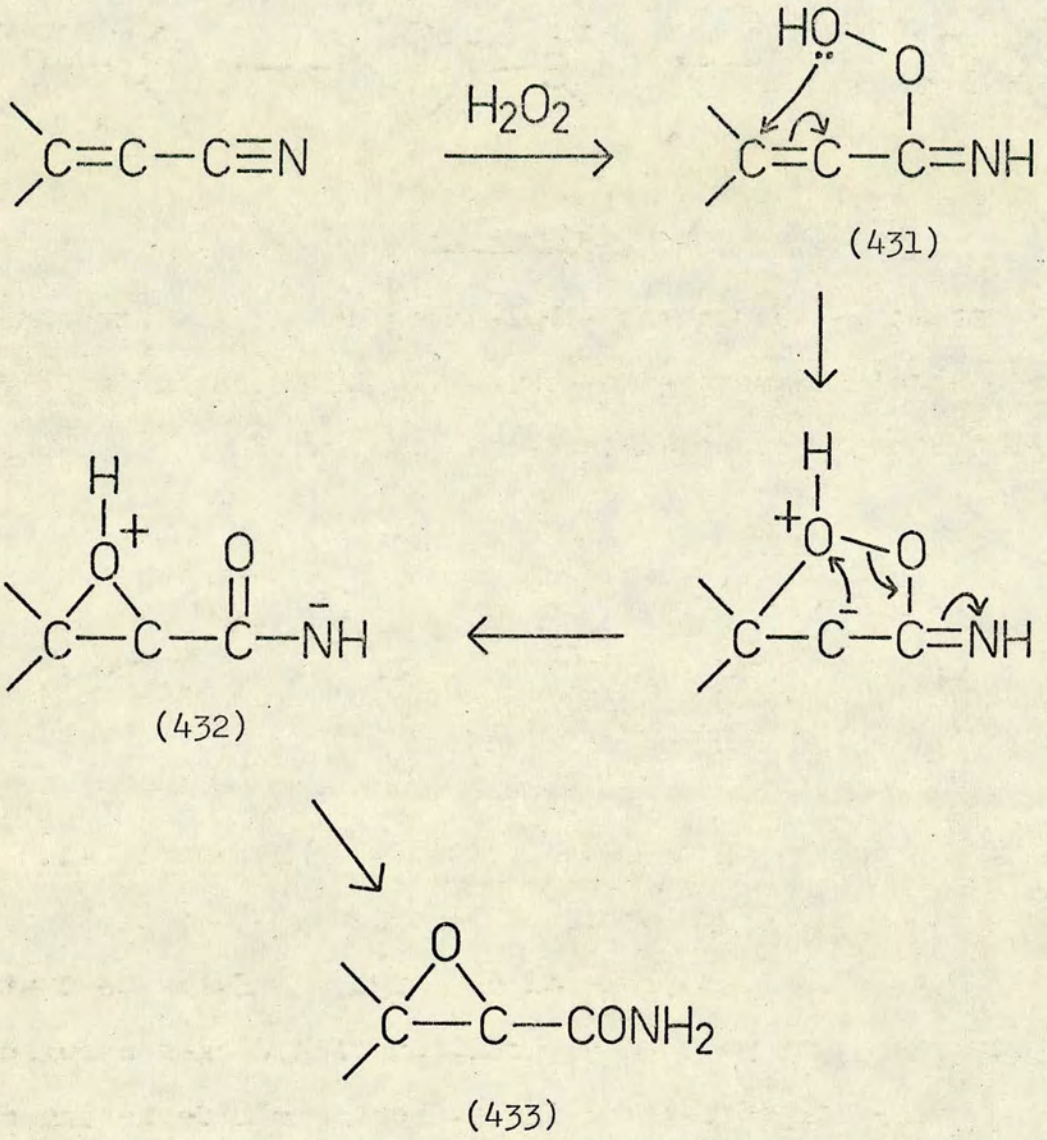
3.4. The Epoxidation of the 2-Nitrobenzylidene Derivatives of Active Methylene Compounds

Peracids, for example perbenzoic acid, are suitable reagents for the direct oxidation of alkylated olefins to

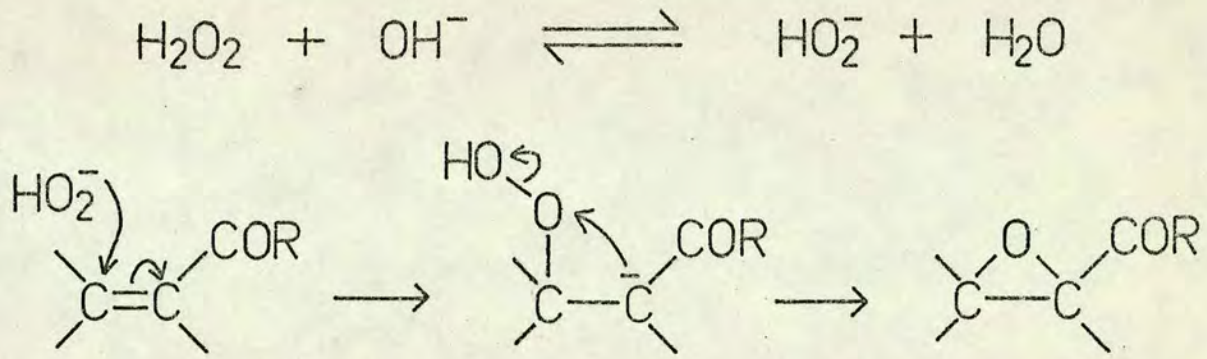
Scheme 68

epoxides (Scheme 68). However if the substituents are electron-withdrawing (e.g. keto, ester, or carboxyl groups) the reaction is either slow or fails completely. The explanation for this is found in the electrophilic character of peroxyacids as demonstrated by Lynch and Pausacker[164] in the epoxidation of trans-stilbene. The rate of oxidation using para-nitroperbenzoic acid is 30 times faster than with para-methoxyperbenzoic acid. The electron-withdrawing nitro-group enhances the electrophilic character of the reagent compared to the electron-releasing methoxy-group so increasing the rate of reaction. Electron-withdrawing groups in the olefin reduce the electron density at the carbon to carbon double bond rendering it less susceptible to reaction with an electrophilic reagent.

For α,β-unsaturated carbonyl compounds hydrogen peroxide under basic conditions is the recommended reagent since it functions[165a] by nucleophilic attack by hydroperoxy anion at the double bond (Scheme 69), and has the advantage of being specific for the ethylenic linkage. In some cases hydrogen peroxide will convert α,β-unsaturated nitriles into epoxy-amides. Thus, benzylidenephenylacetonitrile (426) affords[166]

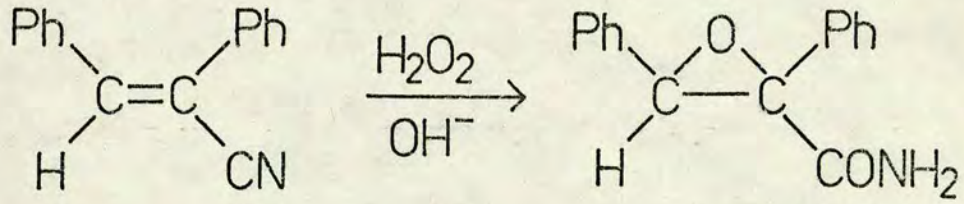


Scheme 70



Scheme 69

1-carbamoyl-1,2-diphenylethylene oxide (427) on treatment with alkaline hydrogen peroxide. The reaction[167] of ethyl 2-nitrobenzylidenecyanoacetate (413c) with hydrogen peroxide



(426) (427)

in the presence of the base, trisodium phosphate, was employed for the synthesis of 1-carbamoyl-1-ethoxycarbonyl-2-(2-nitrophenyl)ethylene oxide (429d). Evidence that these reactions proceed by addition of hydrogen peroxide to the cyano-group affording the hydroperoxyimide intermediate (431) has been obtained by Payne and Williams.[168] Intramolecular oxidation-reduction of the intermediate (431) (Scheme 70) and tautomerisation then explain the formation, [(431)→(432)→(433)], of the epoxyamide (433). The ability of hydroperoxyimide intermediates of the type (431) to function as oxidising agents was utilised by Payne and his coworkers[169] to develop a method of epoxidation in which alkaline hydrogen

peroxide is added to an olefin in the presence of a nitrile. Thus, the reaction of styrene (434) with hydrogen peroxide

(434) (435)

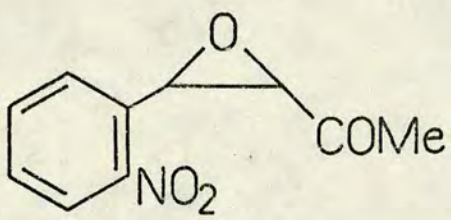
at 70° in the presence of acetonitrile at pH 7.5 affords styrene oxide (435). The clear advantage of this method is that it permits the epoxidation of sensitive molecules to be carried out under nearly neutral, instead of strongly alkaline, conditions.

The attempted preparation of 1,1-diacetyl-2-(2-nitrophenyl)ethylene oxide (430a) by stirring 2-nitrobenzylideneacetylacetone (415a) in ethanol at 70° with 30% hydrogen peroxide and trisodium phosphate gave a gum from which no solid material could be obtained. When the reaction conditions were modified by stirring the benzylidene derivative (415a) with 30% hydrogen peroxide in the presence of benzonitrile at room temperature, work up yielded a multi-component gum whose main constituent was unreacted 2-nitrobenzylideneacetylacetone (415a). The use of 50% hydrogen peroxide in the presence of benzonitrile produced the same result.

Marmor[170] has demonstrated that aqueous sodium hypochlorite is an excellent reagent for the epoxidation of α,β-unsaturated compounds. Thus, reaction of benzylidene acetophenone (436) in pyridine solution with aqueous sodium hypochlorite affords an excellent yield of the epoxide (437).

(436) (437)

The advantages claimed[170] for this procedure are that the reaction is complete in a few minutes whereas hydrogen peroxide requires several hours before oxidation is complete, and that the reagent is less hazardous to use than hydrogen peroxide. However the present author found that stirring a solution of 2-nitrobenzylideneacetylacetone (415a) in pyridine at room temperature with aqueous sodium hypochlorite for only one minute gave a dark mixture. Work-up gave a dark gum whose ^{1}H n.m.r. spectrum showed it to be a mixture of the unreacted benzylidene compound (415a) and cis-1-acetyl-2-(2-nitrophenyl)ethylene oxide (438). Signals at τ 7.54 and 7.90



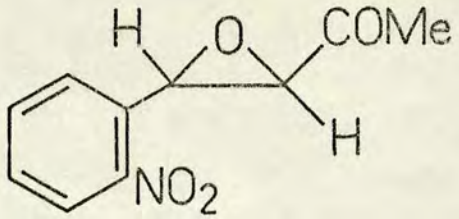
(438)

correspond to the methyl groups of 2-nitrobenzylideneacetylacetone (415a) whose olefinic hydrogen is not observed since it absorbs in the region of the aromatic protons. A pair of doublets centred at τ 5.29 and 5.84 can be assigned to the cis-acetylethylene oxide (438) on the basis of the magnitude of the coupling constant (cf. page 147). This assignment is consistent with the presence of a singlet at τ 8.04 attributable to the methyl protons of the cis-epoxide (438). Although

all of the starting material is not being consumed, the formation of (438) shows that epoxidation does occur under these conditions but is accompanied by loss of an acetyl group. Marmor[170] found that the attempted epoxidation of 1,4-naphthaquinone (439) to (440) in pyridine solution using

(439) (440)

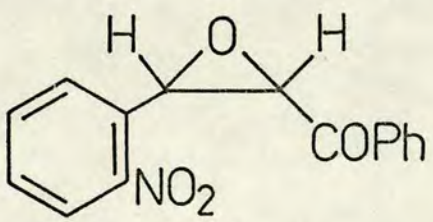
aqueous sodium hypochlorite also resulted in over-reaction. However, reaction of the quinone (439) in dioxan solution with aqueous sodium hypochlorite resulted in the isolation of an excellent yield of the epoxide (440) thus illustrating the milder character of hypochlorite oxidation under these conditions. Consequently, the epoxidation of 2-nitrobenzylideneacetylacetone (415a) with aqueous sodium hypochlorite was undertaken in dioxan solution. Work-up of the reaction mixture after 5 min produced a red gum whose ^{1}H n.m.r. spectrum contained signals ascribable to the benzylidene starting material (415a) and cis-1-acetyl-2-(2-nitrophenyl) ethylene oxide (438). In addition the spectrum showed a pair of doublets at τ 5.40 and 6.58 and a singlet at τ 7.74 which correspond to the ^{1}H n.m.r. absorption reported[145] for trans-1-acetyl-2-(2-nitrophenyl)ethylene oxide (370). Prolonged reaction with sodium hypochlorite in dioxan gave the same mixture of starting material (415a) and cis and trans-acetyl-



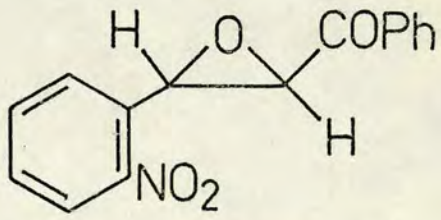
(370)

epoxides (438) and (370). The ^{1}H n.m.r. spectra of the products of the hypochlorite oxidation of 2-nitrobenzylidene-acetylacetone (415a) showed no trace of absorption attributable to the required diacetylethylene oxide (430a).

Reaction of 2-nitrobenzylidenebenzoylacetone (411c) in pyridine with sodium hypochlorite at room temperature gave the known[145,150] cis-1-benzoyl-2-(2-nitrophenyl)ethylene oxide (380) and a gum whose ^{1}H n.m.r. spectrum indicated the presence of three components. Singlets at τ 1.83 and 7.56 are attributable to the olefinic and methyl protons of the benzylidene starting material (411c). Comparison with the ^{1}H n.m.r. spectrum of an authentic sample[145] also demonstrated the presence of trans-1-benzoyl-2-(2-nitrophenyl)ethylene oxide (367). In addition singlets at τ 4.89 and 7.61



(380)



(367)

can be attributed to the presence of a minor amount of the desired product (428c). Despite the milder conditions, the same mixture was formed by the hypochlorite oxidation of the benzylidene compound (411c) in dioxan.

The attempts to epoxidise the benzylidene derivatives (415a) and (411c) clearly indicated that deacylation was occurring under the reaction conditions. Because of this it was decided to investigate the epoxidation of 2-nitrobenzylidenedibenzoylmethane (411e) from which loss of a benzoyl group might be less easy. Initially, oxidation of the benzylidene derivative (411e) was attempted using meta-chloroperbenzoic acid, one of the more active peracids, but this gave only the starting material in high yield (73%). Reaction of the benzylidene compound (411e) for 12h with 30% hydrogen peroxide in the presence of potassium hydrogen carbonate as the base was also ineffective. The use of 30% hydrogen peroxide in conjunction with trisodium phosphate likewise gave only unreacted starting material (411e). The isolation of dibenzoylmethane (410e) from the mother liquors in this reaction indicates that some hydrolysis of 2-nitrobenzylidenedibenzoylmethane (411e) had also occurred. In contrast to its inertness to peracid oxidation however, brief (10 min) reaction of 2-nitrobenzylidenedibenzoylmethane (411e) at room temperature with aqueous sodium hypochlorite in pyridine gave the desired 1,1-dibenzoyl-2-(2-nitrophenyl) ethylene oxide (428e) in excellent yield. The structure of this product is consistent with its i.r. spectrum which contains carbonyl and nitro-group absorption and with its ^{1}H n.m.r. spectrum which shows a one proton singlet at τ 4.70 attributable to the benzylic hydrogen. Confirmation of the epoxide structure (428e) was provided by the product's mass spectral and combustion analysis. Reaction of 2-nitrobenzylideneacetophenone (411a) with aqueous sodium hypochlorite in

pyridine for 5 min also afforded trans-1-benzoyl-2-(2-nitrophenyl)ethylene oxide (428a) in good yield.

The ^{1}H n.m.r. spectrum of the product obtained in moderate yield by the pyridine catalysed hypochlorite oxidation of 2-nitrobenzylidenebenzoylacetonitrile (411d) showed only a single one proton absorption in the epoxide region, consistent with its formulation as either the cis or the trans form of the epoxide (428d). When ethyl 2-nitrobenzylidenebenzoylacetate (411b) dissolved in pyridine was reacted with aqueous sodium hypochlorite for 10 min 1-benzoyl-1-ethoxycarbonyl-2-(2-nitrophenyl)ethylene oxide (428b) was obtained as a red oil. The structure of this product is assigned on the basis of its spectral properties. Mass spectral analysis gave the correct molecular weight and its i.r. spectrum contained absorption bands attributable to a nitro-group and ester and ketonic carbonyl groups. However the ^{1}H n.m.r. spectrum of the oil contained two one proton singlets at τ 4.70 and 4.89 and showed multiple methylene and methyl absorption associated with two distinct ethyl groups. These features demonstrate that the oil is in fact a mixture of the cis and the trans forms of the epoxide (428b) although the ^{1}H n.m.r. spectrum of the benzylidene precursor (411b) showed the presence of only one of the two possible geometrical isomers. In contrast, the attempted pyridine catalysed hypochlorite oxidation of ethyl 2-nitrobenzylideneacetoacetate (413b) resulted only in the recovery of the starting material (413b). Prolonging the reaction time and using dioxan as solvent did not succeed in effecting the oxidation and again the benzylidene derivative

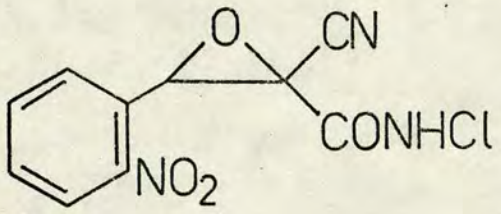
(413b) was recovered unchanged.

The reaction of diethyl 2-nitrobenzylidenemalonate (413a) with aqueous sodium hypochlorite in the presence of pyridine gave the corresponding epoxide (429a) as an oil for which satisfactory i.r., ^{1}H n.m.r. and mass spectral data were obtained.

In contrast to its reaction with alkaline hydrogen peroxide which affords[167] 1-carbamoyl-1-ethoxycarbonyl-2-(2-nitrophenyl)ethylene oxide (429d), ethyl 2-nitrobenzylidenecyanoacetate (413c) reacted with aqueous sodium hypochlorite in pyridine to give 1-cyano-1-ethoxycarbonyl-2-(2-nitrophenyl)ethylene oxide (429c) in moderate yield. Repetition of this oxidation in dioxan gave the epoxide (429c) in slightly improved yield. Spectral data and elemental analysis confirmed the structure of the product (429c) whose ^{1}H n.m.r. spectrum demonstrated the presence of only one of the two possible geometrical isomers.

1-Carbamoyl-1-cyano-2-(2-nitrophenyl)ethylene oxide (430c) was obtained in only low yield by reacting 2-nitrobenzylidenecyanoacetamide (415c) with aqueous sodium hypochlorite in pyridine solution. The product (430c) gave the correct elemental analysis and showed spectral properties consistent with the assigned structure with the exception of its mass spectrum, the parent peak in which occurred inexplicably at m/e 236, three mass units greater than the molecular weight of the epoxide (430c). Repetition of the hypochlorite epoxidation of the benzylidene derivative (415c) in dioxan gave the epoxide (430c) in slightly

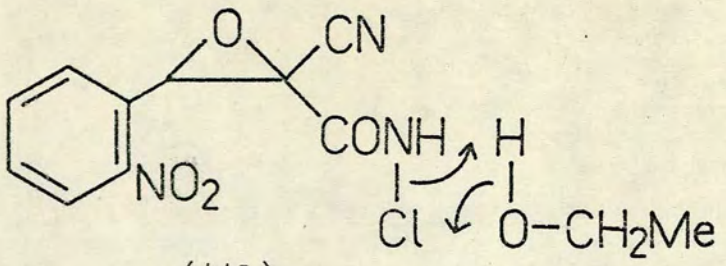
improved yield. Acidification of the alkaline aqueous phase in this oxidation gave a product whose i.r. spectrum showed the presence of a nitro-group, a carbonyl group and a single NH absorption at 3200 cm^{-1}. No structural information was available from the mass spectrum of this product which showed peaks of no higher mass than m/e 135, although the finding that it afforded the epoxide (430c) on crystallisation from ethanol indicated that it had a closely related structure. The unknown compound gave a negative test for ionisable chlorine when it was treated with a solution of silver nitrate in acetonitrile but it gave a positive test for chlorine when subjected to the Lassaigne test. Although a definitive proof of structure was not undertaken, the elemental analysis and spectral and chemical properties of the unknown solid are fully consistent



(441)

with the N-chloro-amide structure (441). The known[171] reaction of amides with hypochlorite ion to yield N-chloro-amides lends support to the structure (441) although N-halo derivatives of primary amides are rarely isolated, and tend to undergo the Hofmann rearrangement to the amine (Scheme 71). The known[172] oxidation of primary alcohols by N-haloamides accounts for the isolation of the epoxide after crystallisation of the N-halo-amide (441) from ethanol. The course of this

(a)



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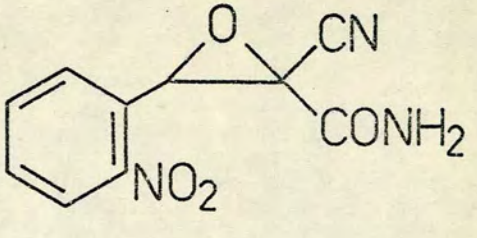
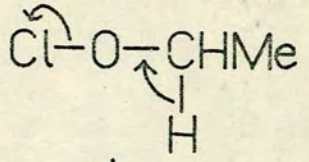
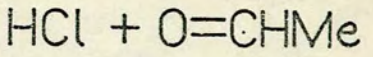
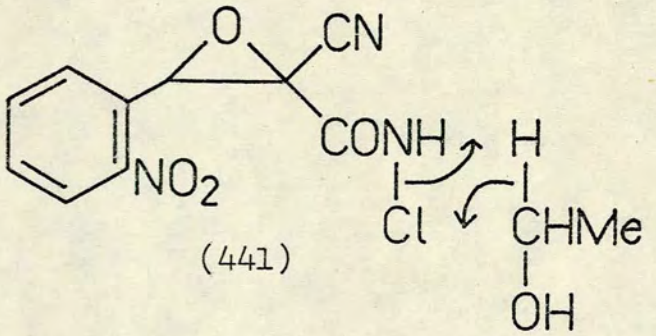


(430c)

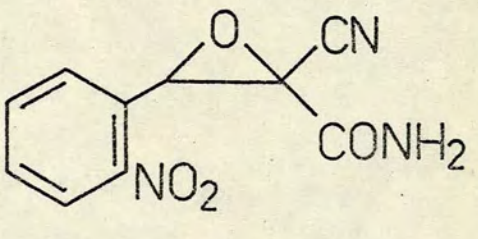




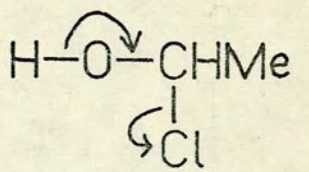
(b)

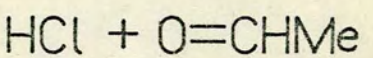


(441)

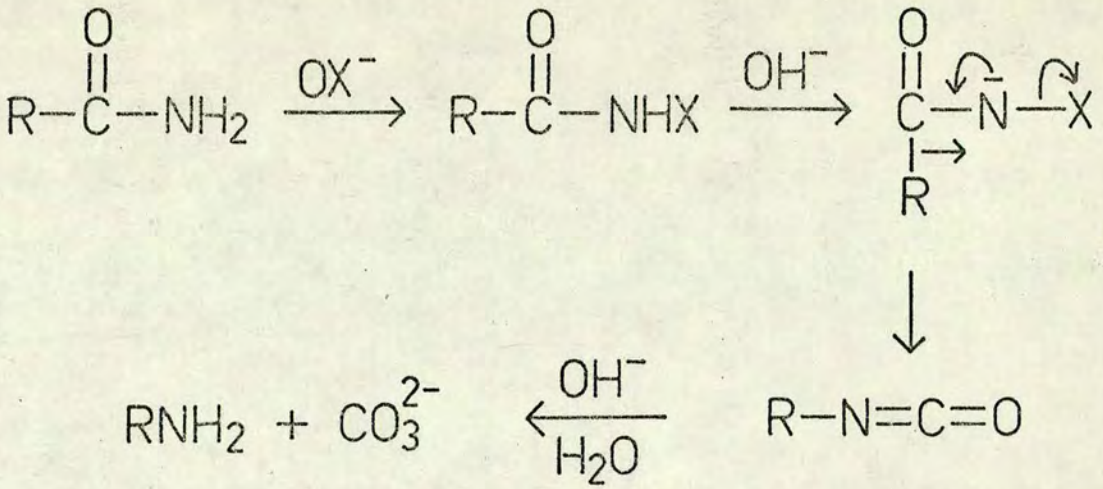


(430c)





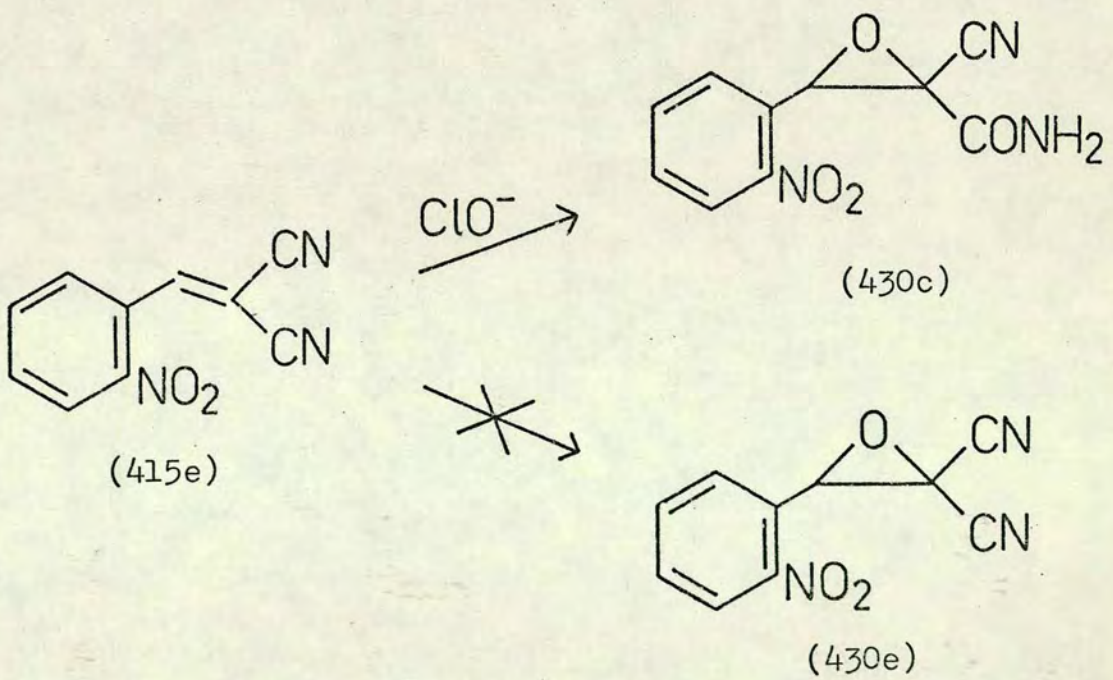
Scheme 72



Scheme 71

transformation can be formulated as shown in Scheme 72(a) involving chlorination of the alcoholic hydroxyl group. However the mechanism of the oxidation process has not been fully elucidated[172] so that chlorination at carbon [Scheme 72(b)] is also a possibility.

The reaction of 2-nitrobenzylidenemalononitrile (415e) with hypochlorite-pyridine at room temperature gave not the expected dicyanoepoxide (430e) but the amidocyanoepoxide

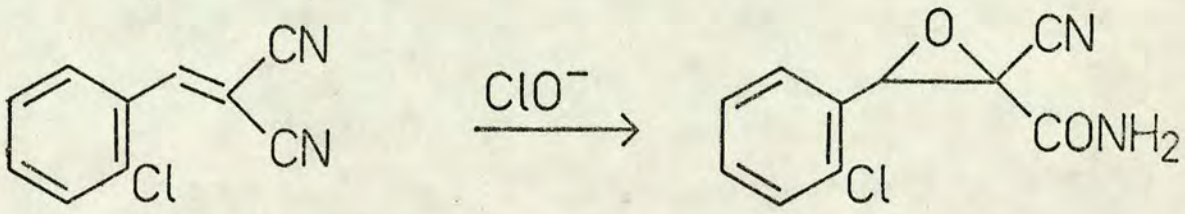


(415e)

(430c)

(430e)

(430c). There is precedent for the concomitant hydrolysis of the cyano-group involved in this reaction. Thus, treatment of 2-chlorobenzylidenemalononitrile (442) with



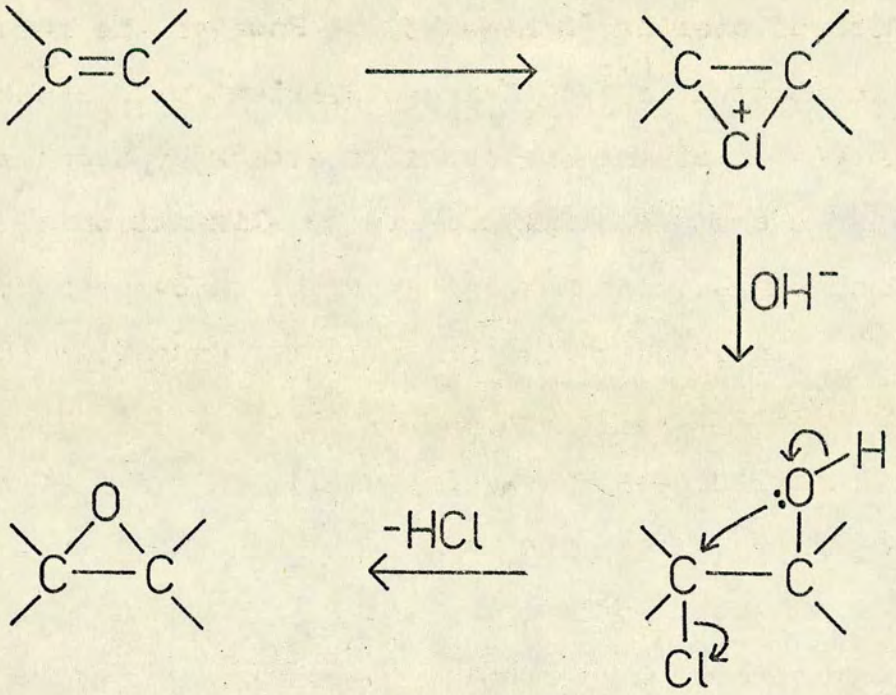
(442) (443)

aqueous sodium hypochlorite is known[173] to yield the epoxyamide (443) as the major product. In contrast to the concurrent epoxidation and hydrolysis involved in the conversion of α,β-unsaturated nitriles into epoxyamides by perhydroxyl ion[168,174] (cf. page 158), the oxidation and hydrolysis induced by hypochlorite ion are thought[173] to be consecutive processes.

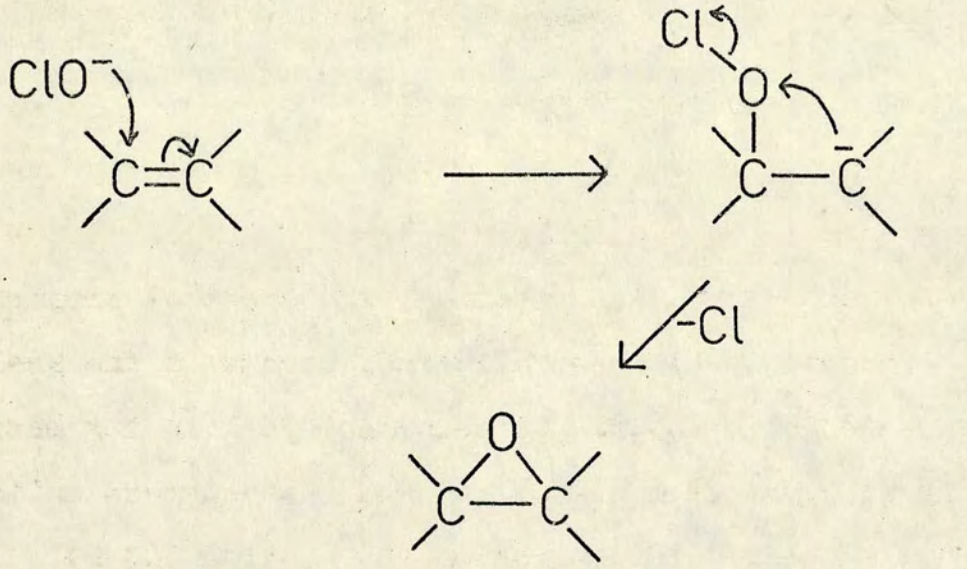
Treatment of 2-nitrobenzylidenemalonamide (415d) with aqueous sodium hypochlorite in dioxan gave an almost quantitative yield of 2-nitrobenzaldehyde. Pommeret and Robert[175] have successfully performed epoxidations in acidic media. However, the attempted oxidation of the benzylidene derivative (415d) under such conditions again resulted in the isolation of only 2-nitrobenzaldehyde.

The foregoing studies clearly demonstrate that hypochlorite oxidation of the readily available 2-nitrobenzylidene derivatives of active methylene compounds provides an efficient general route to the corresponding epoxides.

There is a considerable weight of evidence[165b] in favour of chloronium ion intermediates in the hypochlorite



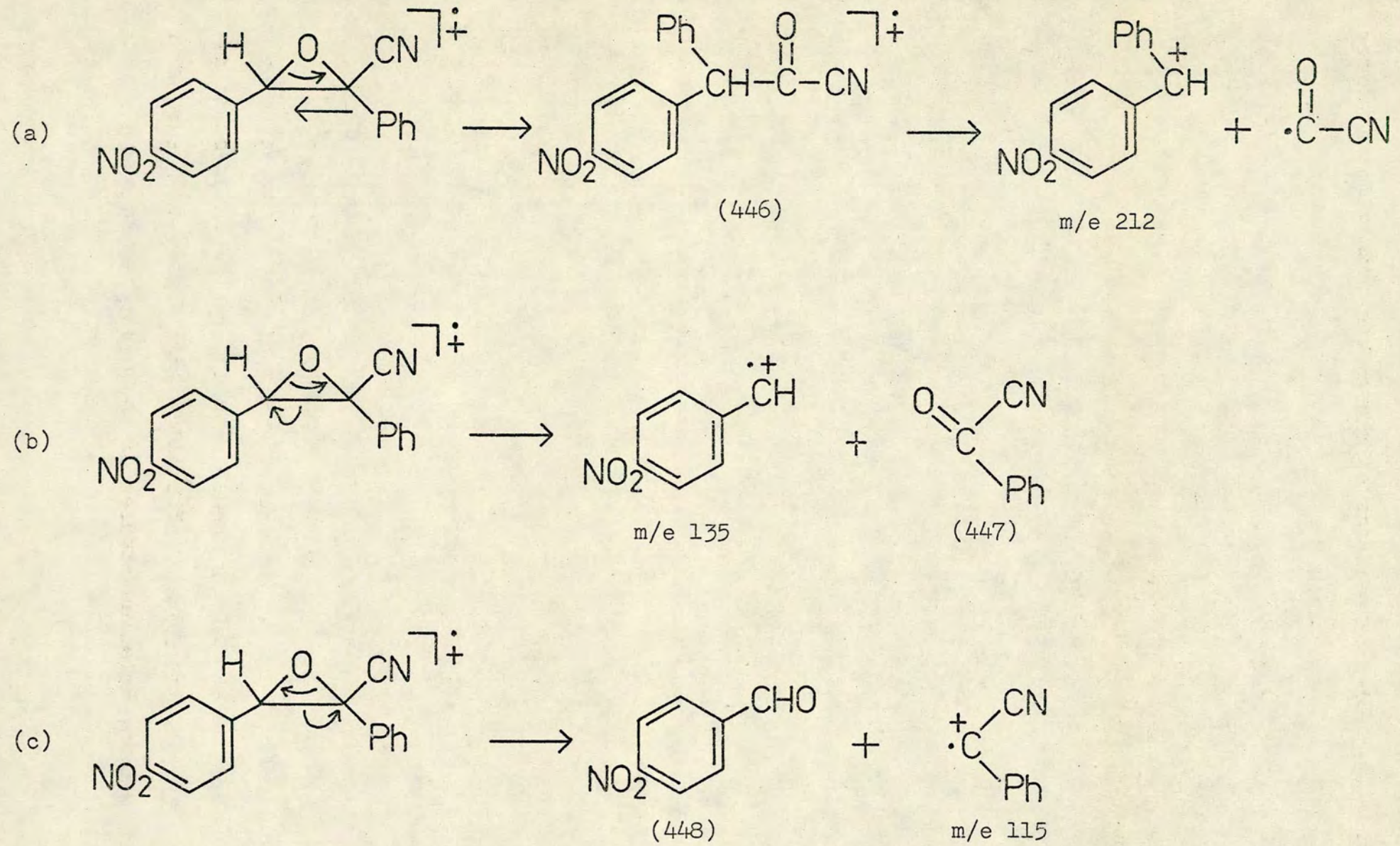
Scheme 73



Scheme 74

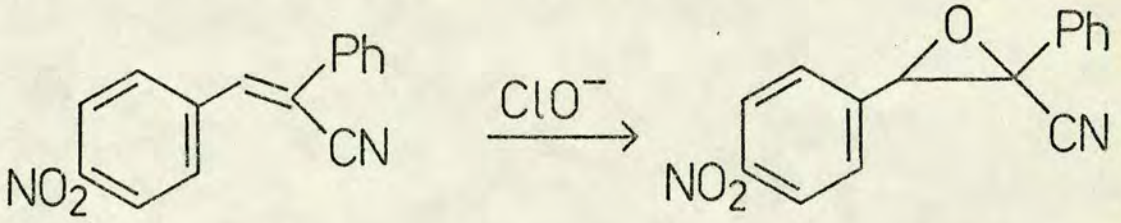
oxidation of olefins (Scheme 73). However the results of more recent studies[173,176] are consistent with a mechanism (Scheme 74) involving nucleophilic attack by hypochlorite anion and subsequent ring closure by elimination of chloride ion in an analogous manner to epoxidation by perhydroxyl ion.[165a] In agreement with the latter mechanism (Scheme 74) hypochlorite oxidation was unsuccessful in the case of 2-nitrobenzylidenedeoxybenzoin (411f) and 2-nitrobenzylidene-propiophenone (411g) even under forcing conditions. The electron-releasing phenyl and methyl groups in these benzylidene derivatives will render the ethylenic linkage less susceptible to nucleophilic attack by hypochlorite ion.

In contrast to the inertness of the compounds (411f and g), 2-nitrobenzylidenephenylacetonitrile (415b) was readily oxidised by pyridine-hypochlorite to 1-cyano-2-(2-nitrophenyl)-1-phenylethylene oxide (430b) in almost quantitative yield. The success of this reaction must be due to the greater activation of the double bond by the cyano group compared to the benzoyl group in (411f). With the exception of the mass spectrum, the spectral properties of the product (430b) were fully in accord with the assigned structure (430b). However, the parent peak in its mass spectrum occurred at m/e 250, that is sixteen mass units less than the molecular weight of the epoxide (430b). Recording the spectrum at successively lower ionising voltages down to 10eV failed to show the presence of the parent ion. To ascertain if this mass spectral behaviour could be attributed to the presence of the ortho-nitro-


(a)
H
O
CN
Ph
NO2
Ph
O
CH–C–CN
NO2
(446)
Ph
CH
NO2
m/e 212
O
·C–CN
(b)
H
O
CN
Ph
NO2
·+
CH
NO2
m/e 135
O
CN
C
Ph
(447)
(c)
H
O
CN
Ph
NO2
CHO
NO2
(448)
CN
·C
Ph
m/e 115

Scheme 75

group the isomeric 1-cyano-2-(4-nitrophenyl)-1-phenylethylene oxide (445) was synthesised by the sodium methoxide catalysed

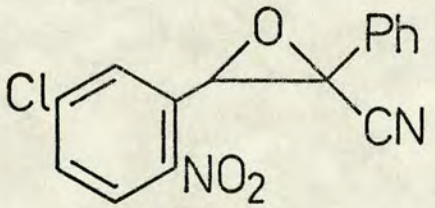


(444) (445)

condensation of 4-nitrobenzaldehyde with phenylacetonitrile to give 4-nitrobenzylidenephenylacetonitrile (444) followed by pyridine-hypochlorite epoxidation. The structure of the product (445) was established by its elemental analysis and spectral properties, including its mass spectrum which exhibited a strong parent ion at m/e 266. Major fragment ions at m/e 212, 135 and 115 can also be rationalised on the basis of the known[177] cracking pattern of epoxides (Scheme 75). Step (a) involves opening of the epoxide ring with migration of the phenyl group and cleavage of the resultant ketone (446). In steps (b) and (c) ring-opening occurs with the elimination of the fragments (447) and (448) respectively. The main fragmentations in the mass spectrum of the 2-nitrophenylethylene oxide (430b) occur at m/e 250, 135, 131, 119 and 115. With the exception of the ions corresponding to m/e 135 and 115 (which could arise as indicated in Scheme 75) this cracking pattern cannot be explained by the known modes of mass spectral fragmentation of epoxides and must presumably be due to the involvement of the ortho-nitro-group. The literature does not appear to contain any detailed studies of the mass spectra of

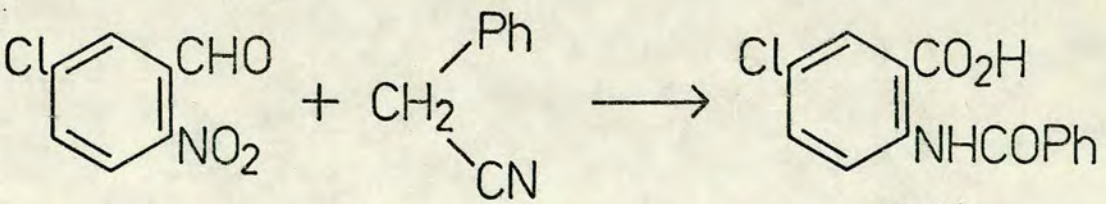
substituted 2-nitrophenylethylene oxides and none of the reported mass spectral studies of 2-nitrobenzene derivatives contain any reference to the primary loss of an oxygen atom. This process in the epoxide (430b) appears to be induced exclusively by electron-impact since heating to the melting point resulted in no decomposition. Possible photo-decomposition of (430b) with loss of oxygen was not investigated.

To gain some insight into the generality of the apparently unique mass spectral properties of the epoxide (430b) it was decided to prepare and examine the mass spectral behaviour of 2-(5-chloro-2-nitrophenyl)-1-cyano-1-phenylethylene oxide (449). However the attempted sodium methoxide

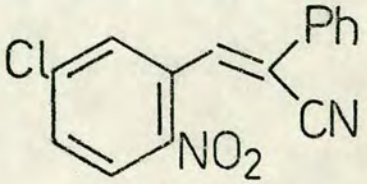


(449)

catalysed condensation of 5-chloro-2-nitrobenzaldehyde with phenylacetonitrile afforded 2-benzamido-5-chlorobenzoic



(450)

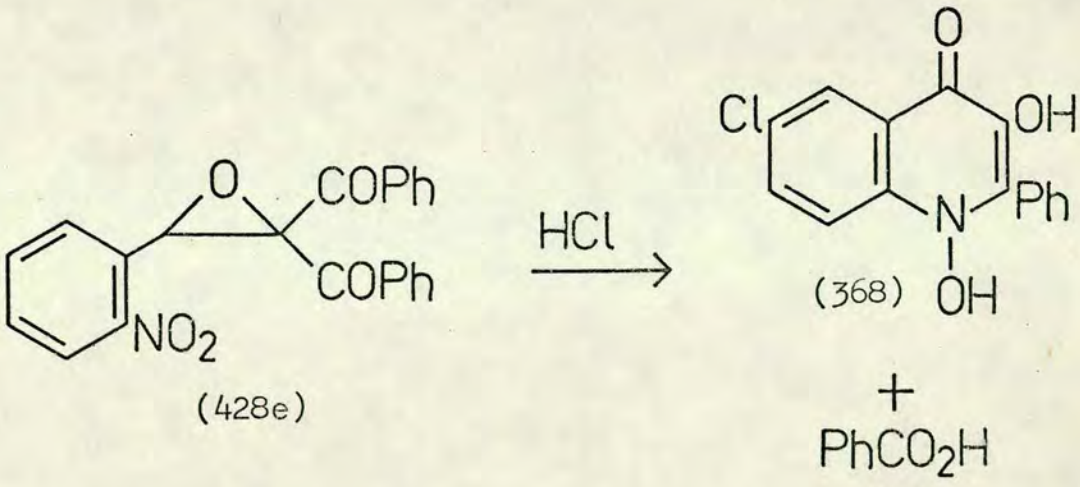


(451)

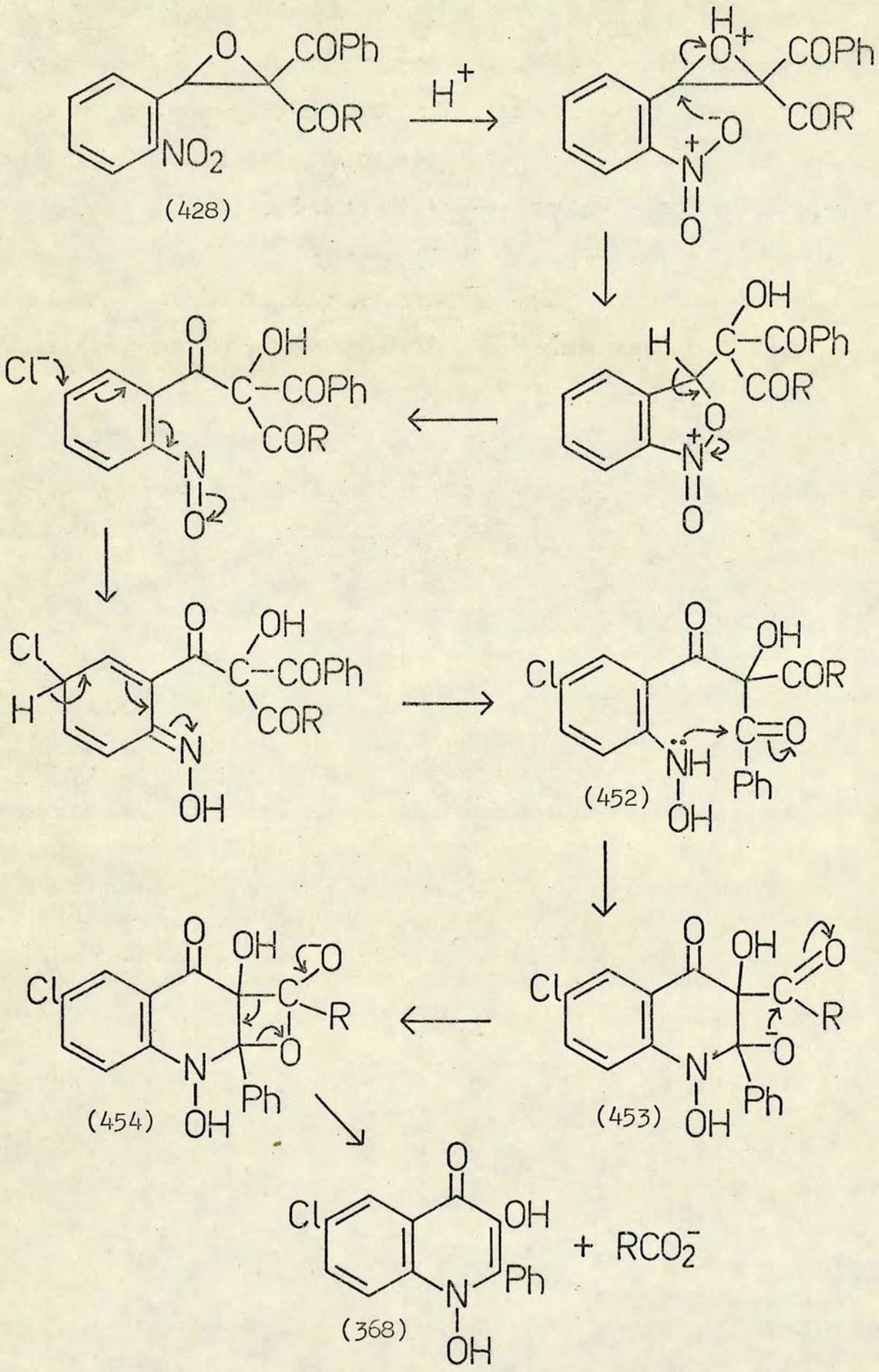
acid (450), rather than the requisite benzylidene derivative (451). The formation of the amide (450) in this condensation is akin to the conversion of the benzylidene derivative (415b) in the presence of alkali into 2-benzamidobenzoic acid (416) (<u>cf.</u> Scheme 66, page 155).

3.5. Reactions of Substituted 2-Nitrophenylethylene Oxides with Hydrogen Chloride

Having developed a general method for the synthesis of diacylated 2-nitrophenylethylene oxides and analogous compounds, attention was next directed to the study of their reactions with hydrogen chloride. Such reactions of the diacylated epoxides (428b and e) and (429a and d) and the related compounds (428d), (429c) and (430b) are of particular interest in that the proposed route to chlorinated 1,3-dihydroxyquinolinones (cf Scheme 62, page 143) is blocked in these epoxides by the presence of the additional substituent. Consequently it was hoped that the study of the hydrogen chloride catalysed reactions of the epoxides (428b, d and e), (429a, c and d) and (430b) might provide insight into the mechanism of nitro-group participation in epoxide ring-opening. These reactions were carried out by leaving a solution of the epoxide in dioxan saturated with hydrogen chloride at room temperature for 80h. Under these conditions 1,1-dibenzoyl-2-(2-nitrophenyl)ethylene oxide (428e) gave mainly unreacted epoxide (428e) together with the 6-



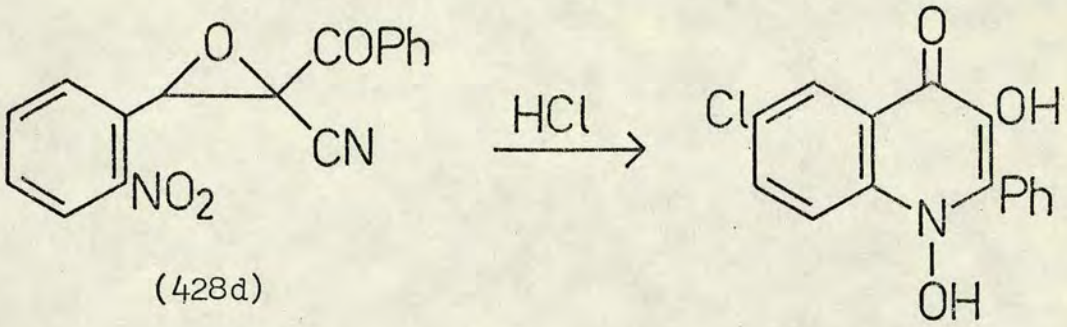
(428e)



Scheme 76

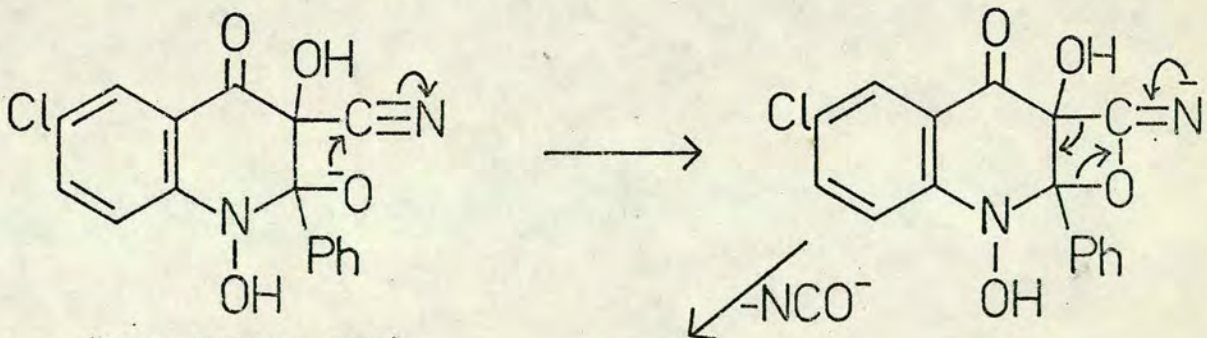
[R = Ph, OEt]

chloroquinolinone (368) and benzoic acid. The formation of these products is explicable by the course shown in Scheme 76 (R=Ph), the benzoic acid arising from the expelled benzoyl group [(453)→(454)→(368); R=Ph]. This mechanism is directly analogous to that invoked[145,146] (Scheme 62, page 143) to rationalise the formation of 6-chloroquinolinones (388) from monoacylated 2-nitrophenylethylene oxides (381). However it is difficult to explain the relative inertness of the epoxide (428e). In contrast, the reaction of 1-benzoyl-1-cyano-2-(2-nitrophenyl)ethylene oxide (428d) with hydrogen chloride afforded an excellent yield of the 6-chloroquinolinone (368), whose formation is rationalised



(428d) (368)

as shown in Scheme 76 (CN for COR), the cyano-group being eliminated from the hydroxylamino intermediate (453, CN for

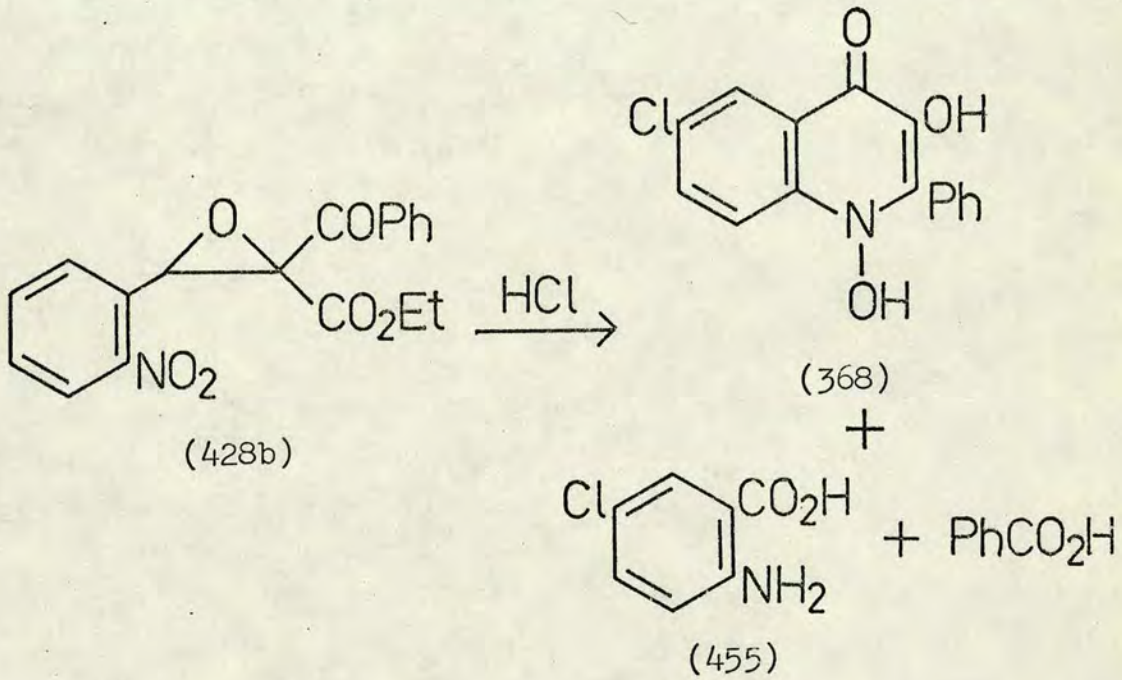


(453, CN for COR) (368)

Scheme 77

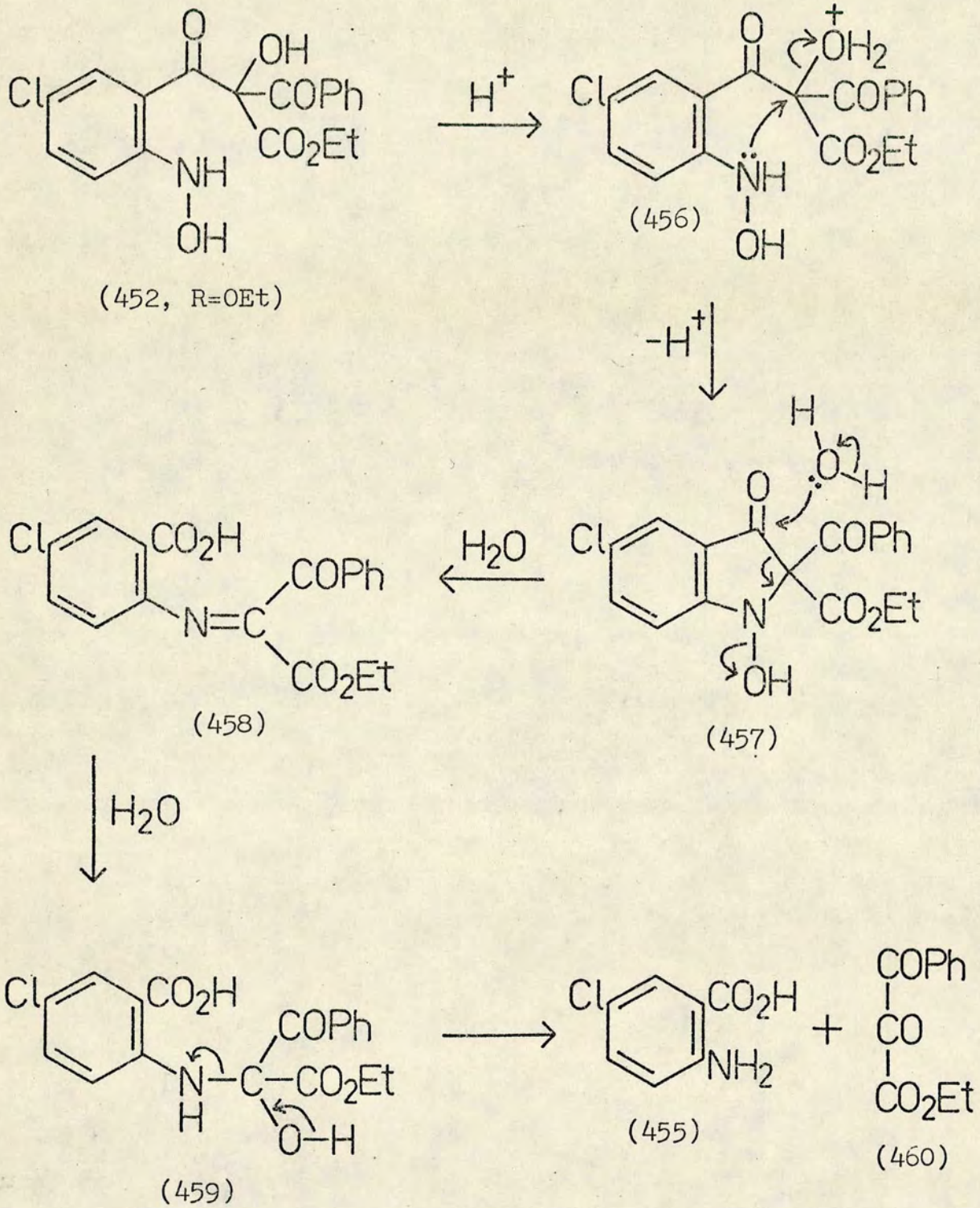
COR) as cyanate ion in the manner indicated in Scheme 77. It is of interest to note that reaction of the epoxide (428d) occurred by exclusive cyclisation through the benzoyl group although hydroxylamino-nitrile condensations are well known (see page 10).

The reaction of 1-benzoyl-1-ethoxycarbonyl-2-(2-nitrophenyl)ethylene oxide (428b) with hydrogen chloride gave



(428b) (368) + (455)

mainly 5-chloroanthranilic acid (455) and benzoic acid together with a smaller amount of the 6-chloroquinolinone (368). The formation of the latter product (368) is again explicable by a course (Scheme 76, R=OEt) involving loss of the ester group [(453)⟶(454)⟶(368); R=OEt]. The isolation of 5-chloroanthranilic acid (455) and benzoic acid is most easily explained by postulating that the reaction follows the course shown in Scheme 76 (R=OEt) as far as the chlorohydroxylamino-intermediate (452; R=OEt) which can either afford the chloroquinolinone (368) or can cyclise in the

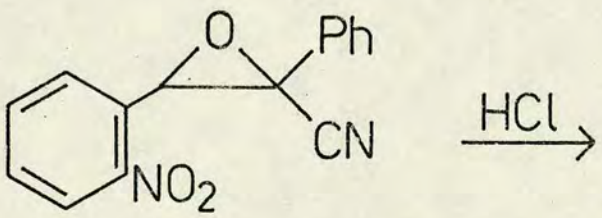

Cl
O
OH
COPh
CO2Et
NH
OH
(452, R=OEt)
H+
+OH2
(456)
-H+
H
O
H
CO2H
N=C
(458)
H2O
(457)
H2O
N
H
(459)
NH2
(455)
CO
(460)

Scheme 78

manner outlined in Scheme 78. Thus, displacement of the protonated hydroxyl group [(456)→(457)] affords the five-membered intermediate (457). Subsequent nucleophilic attack at the carbonyl function in (457) with ring-opening yields the anil (458), hydrolysis of which [(458)→(459)→(455) + (460)] affords 5-chloroanthranilic acid (455) and the diketo-ester (460). Decomposition of (460) under the conditions of work-up would account for the formation of benzoic acid. The step [(457)→(458)] in Scheme 78 is substantiated by the known[162] base-catalysed conversion of 1-hydroxyindolinone (421) into N-oxalylanthranilic acid (425) (cf. Scheme 67, page 155). Although the epoxide (428b) used was a mixture of the two possible geometrical isomers it is of interest that the 6-chloroquinolinone (368) isolated resulted entirely from cyclisation via the benzoyl group (Scheme 76, R=OEt). There was no evidence for any product derived by cyclisation via the ester group, even though hydroxylamino-ester condensations are known (cf. Scheme 8 and page 9). This result demonstrates that there is no preference for cyclisation by reaction with the cis-substituent in the epoxide (428b).

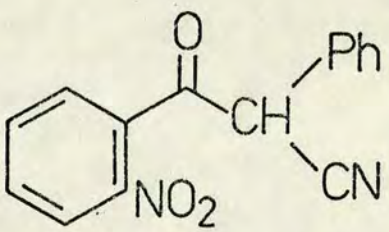
The reaction of the diethoxycarbonyl-epoxide (429a) with hydrogen chloride was undertaken in the hope that cyclisation would be forced to occur through the ester group since this process was not observed in the reaction of the epoxide (428b) in which there was the choice between a benzoyl and an ester group. However, the reaction of the epoxide (429a) with hydrogen chloride resulted in a complex

mixture from which no identifiable products could be isolated. In the acid-catalysed reaction of the benzoylcyano-epoxide (428d) already discussed, although quinolinone formation could theoretically result from cyclisation via either the benzoyl or the cyano group, in practice only cyclisation through the benzoyl group occurred. However in 1-cyano-2-(2-nitrophenyl)-1-phenylethylene oxide (430b) there is no choice and if cyclisation to a quinolinone is to occur it must result from a hydroxylamino-nitrile condensation. The reaction of the cyanophenyl-epoxide (430b) with hydrogen chloride gave two products which were ultimately identified



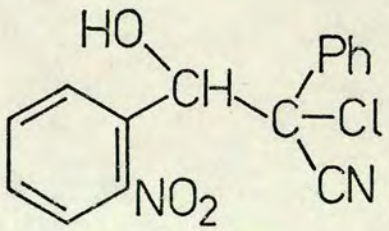
(430b)

HCl →



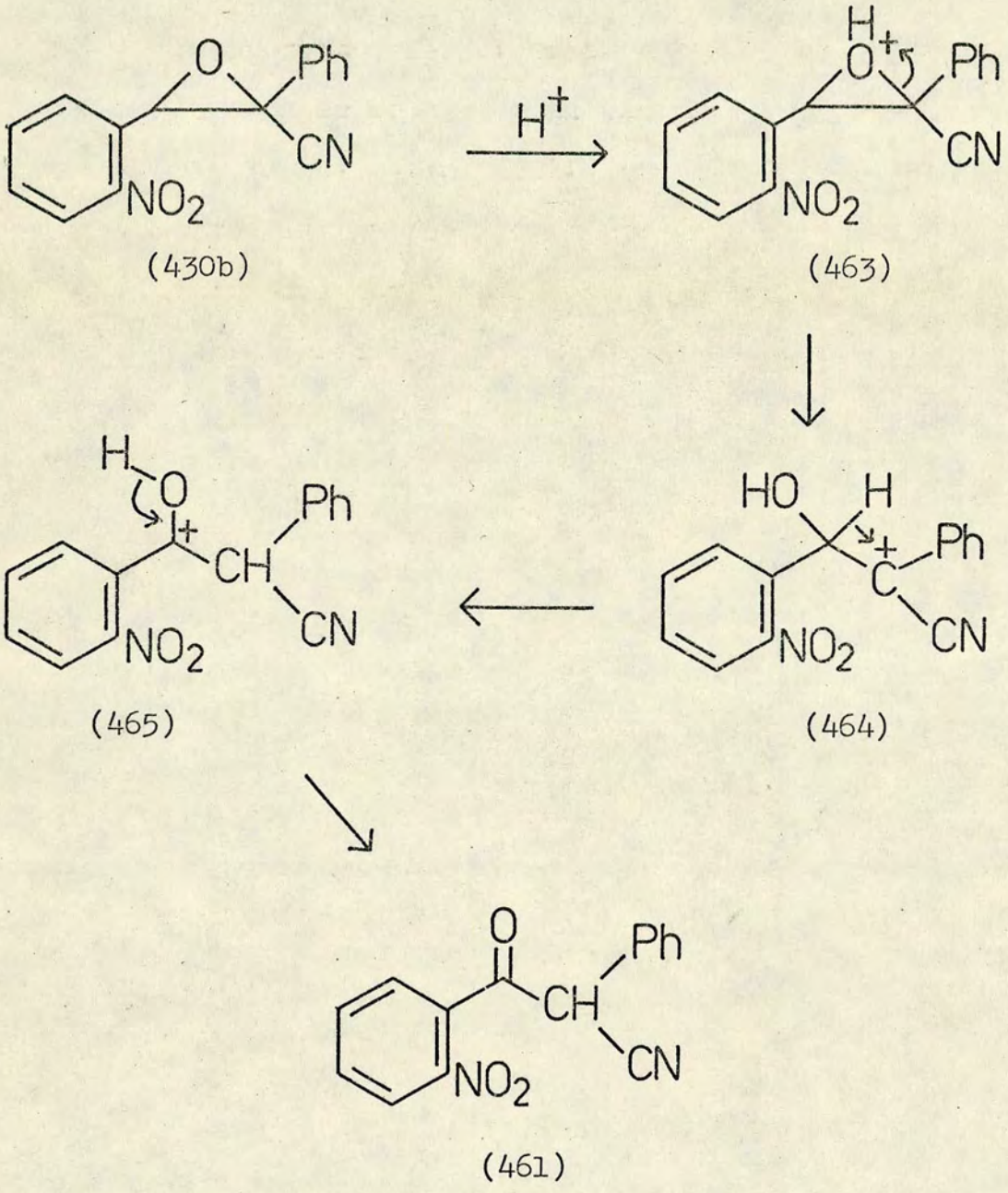
(461)

+



(462)

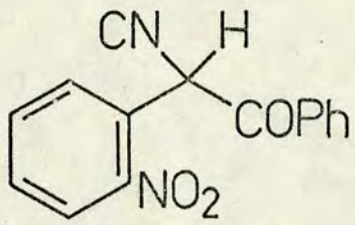
as α-(2-nitrobenzoyl)phenylacetonitrile (461) and the chlorohydrin (462). Also isolated in this reaction was a very small amount of 2-nitrobenzylidenephenylacetonitrile (415b) for which the most probable explanation is that it was an impurity present in the epoxide (430b). The structure



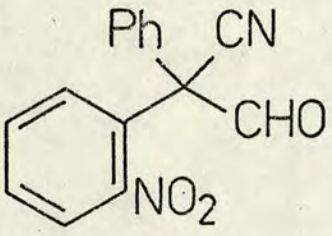
(430b) (463) (464) (465) (461)

Scheme 79

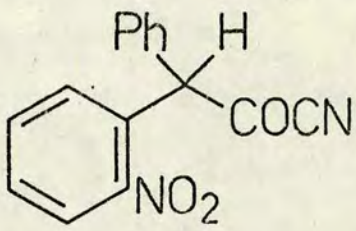
of α-(2-nitrobenzoyl)phenylacetonitrile (461) is based on i.r. and mass spectral evidence. Its formation can readily be explained by the acid-catalysed rearrangement[147] of the epoxide (430b). Thus, ring-opening of the protonated epoxide [(463); Scheme 79] and migration of a hydride ion leads [(463)→(464)→(465)→(461)] to the rearranged product (461). Depending on the mode of scission of the epoxide ring in (463) and on which group migrates there are, in theory,



(467)



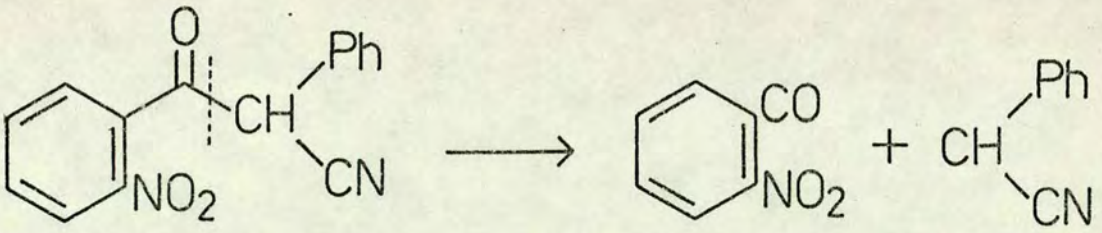
(466)



(468)

four possible rearrangement products [(461), (466), (467) and (468)] of the epoxide (430b). The correctness of the structure (461) is supported by the mass spectrum which shows fragment ions at m/e 150 and 116 corresponding to the fragmentation shown in Scheme 80. None of the other rearrangement products [(466), (467) or (468)] would give rise to these fragments.

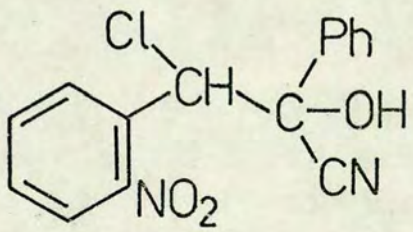
The structure of the chlorohydrin (462) was elucidated on the basis of the following evidence. The molecular formula



(461) m/e 150 m/e 116

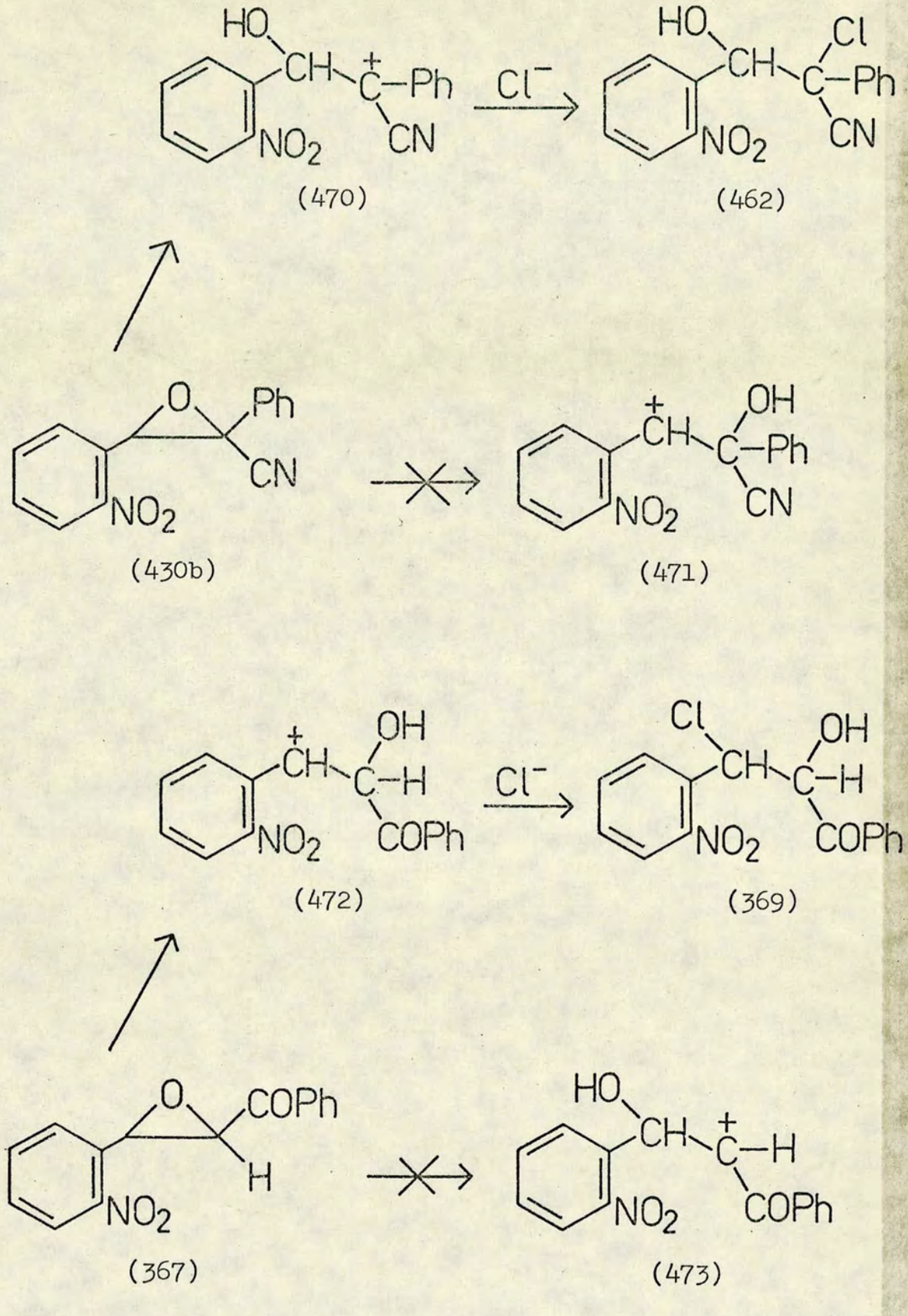
Scheme 80

$C_{15}H_{11}ClN_2O_3$, corresponding to addition of hydrogen chloride to the epoxide (430b), was indicated by elemental and mass spectral analysis. Absorption bands in the i.r. spectrum confirmed the presence of an hydroxyl and a nitro-group. The ^1H n.m.r. spectrum showed coupling between the benzylic and hydroxyl hydrogen atoms which disappeared on shaking with D_2O. The magnitude of the coupling is comparable to that observed[178] between the hydroxyl and methylene protons of ethanol and so excludes the alternative chlorohydrin

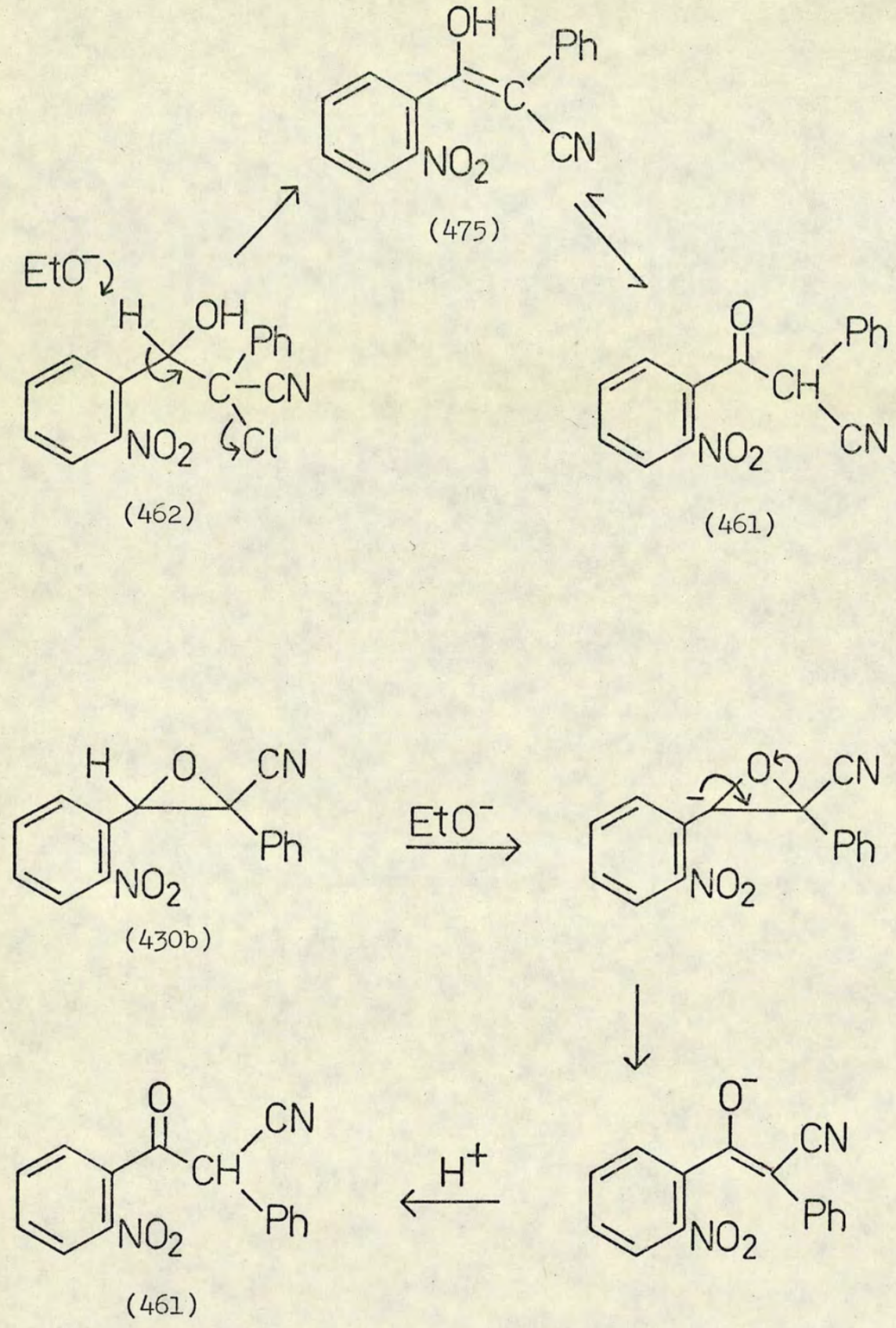


(469)

structure (469). It is of interest that the orientation of the chlorohydrin (462) is the opposite of that observed in the case of the chlorohydrin (369) from trans-1-benzoyl-2-(2-nitrophenyl)ethylene oxide [(367); Scheme 81] (cf. page 141). These alternative modes of chlorohydrin formation can be explained by the relative stabilities of the carbonium



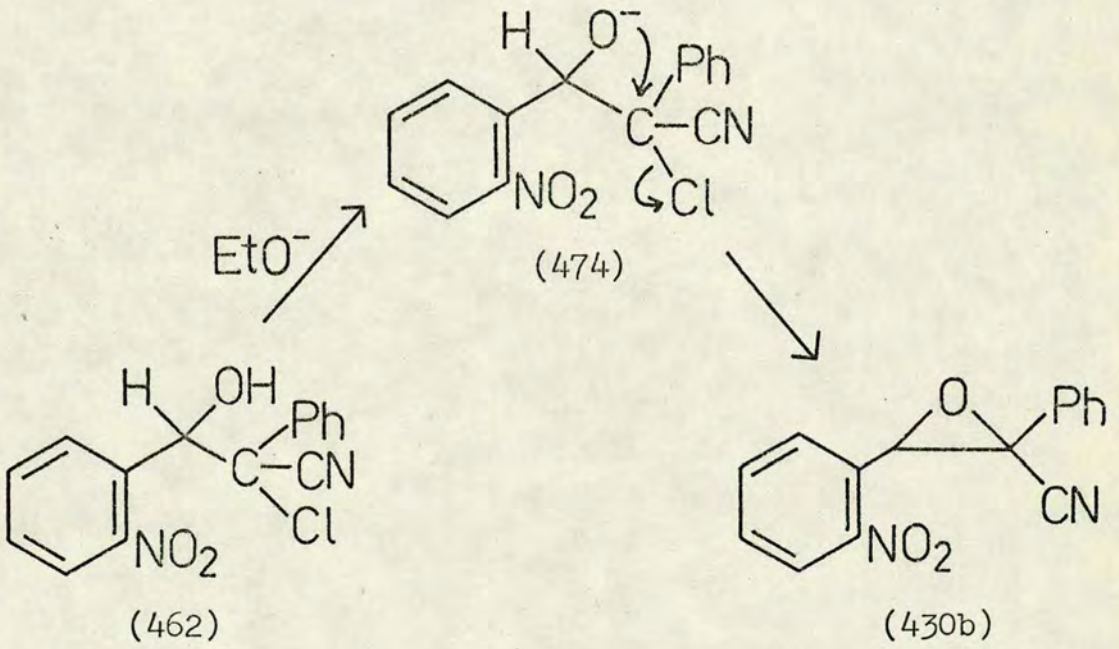
Scheme 81



Scheme 82

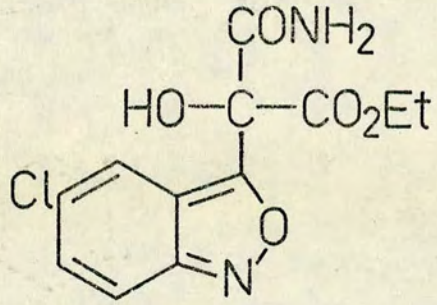
ions [(470) — (473); Scheme 81]. Thus, the formation of the chlorohydrin (462) from (430b) indicates the greater stability of the cyanobenzyl carbonium ion (470) compared to the 2-nitrobenzyl carbonium ion (471), whereas the 2-nitrobenzyl carbonium ion (472) must be more stable than the phenacyl carbonium ion (473) as evidenced by the preferential formation of the chlorohydrin (369).

The chlorohydrin (462), on treatment with ethanolic sodium ethoxide, was reconverted into the epoxide (430b) by elimination [(462)→(474)→(430b)] of hydrogen chloride.



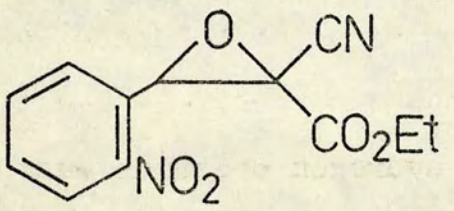
Also formed in this reaction was a minor amount of α-(2-nitrobenzoyl)phenylacetonitrile (461) which can be rationalised by the alternative elimination of hydrogen chloride from the chlorohydrin [(462)→(475)→(461)]. However formation of (461) by the base-catalysed rearrangement[165c] of the epoxide [(430b); Scheme 82] is also a possibility.

The lack of any evidence in the case of the epoxide

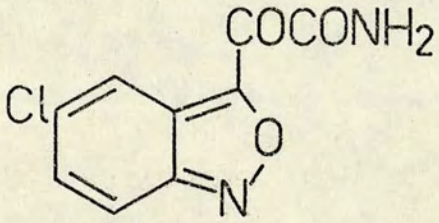


(477)

+

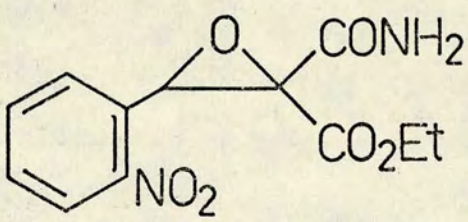


(429c)



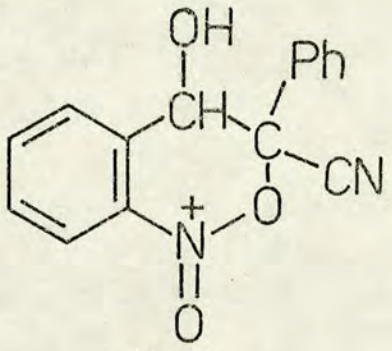
(478)

+



(429d)

(430b) for interaction between the nitro-group and the epoxide ring may be due to the greater stability of the cyanobenzyl carbonium ion (470) over the 2-nitrobenzyl carbonium ion [(471); Scheme 81] (as indicated by the mode of

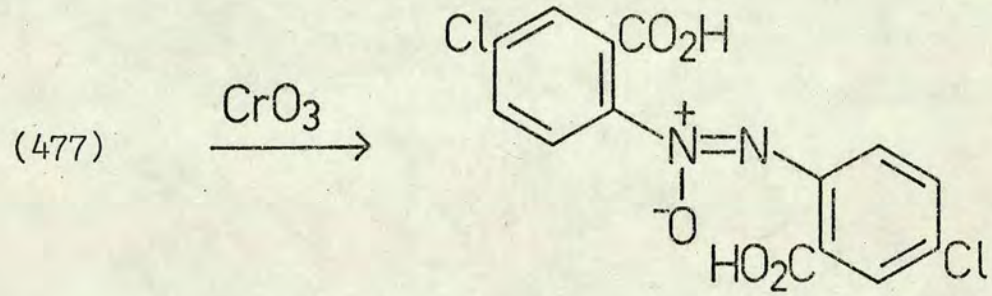


(476)

chlorohydrin formation), and the consequent reluctance of the nitro-group to form the six-membered intermediate (476).

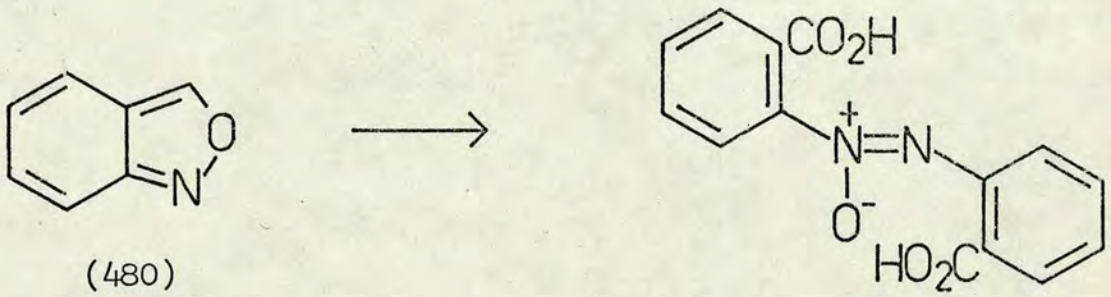
The reaction of 1-cyano-1-ethoxycarbonyl-2-(2-nitrophenyl)ethylene oxide (429c) with hydrogen chloride was of interest since this epoxide contains both a cyano and an ester group which in previous reactions had avoided involvement in cyclisation to quinolinones. This reaction gave, as well as unreacted epoxide (429c) and the amidoester-epoxide (429d), two other products. Although no definitive proof of structure is available as yet, evidence has been obtained which suggests that these products are the anthranil derivatives (477) and (478). Satisfactory elemental and mass spectral analyses were obtained for both of these structures. The i.r. spectrum of the product assigned the structure (477) showed absorption due to an amino-group as well as amide and ester carbonyl absorption. A band at 1680 cm^{-1} is attributed to NH_2 deformation. In further accord with the structure (477) the i.r. spectrum lacked absorption due to a

nitro-group. The ^{1}H n.m.r. spectrum of this product confirmed the presence of an amino-group and the ethyl ester group, and also showed a broad signal assigned to the tertiary hydroxyl group in (477). Chromium trioxide oxidation of the anthranil (477) afforded 4,4'-dichloroazoxy-



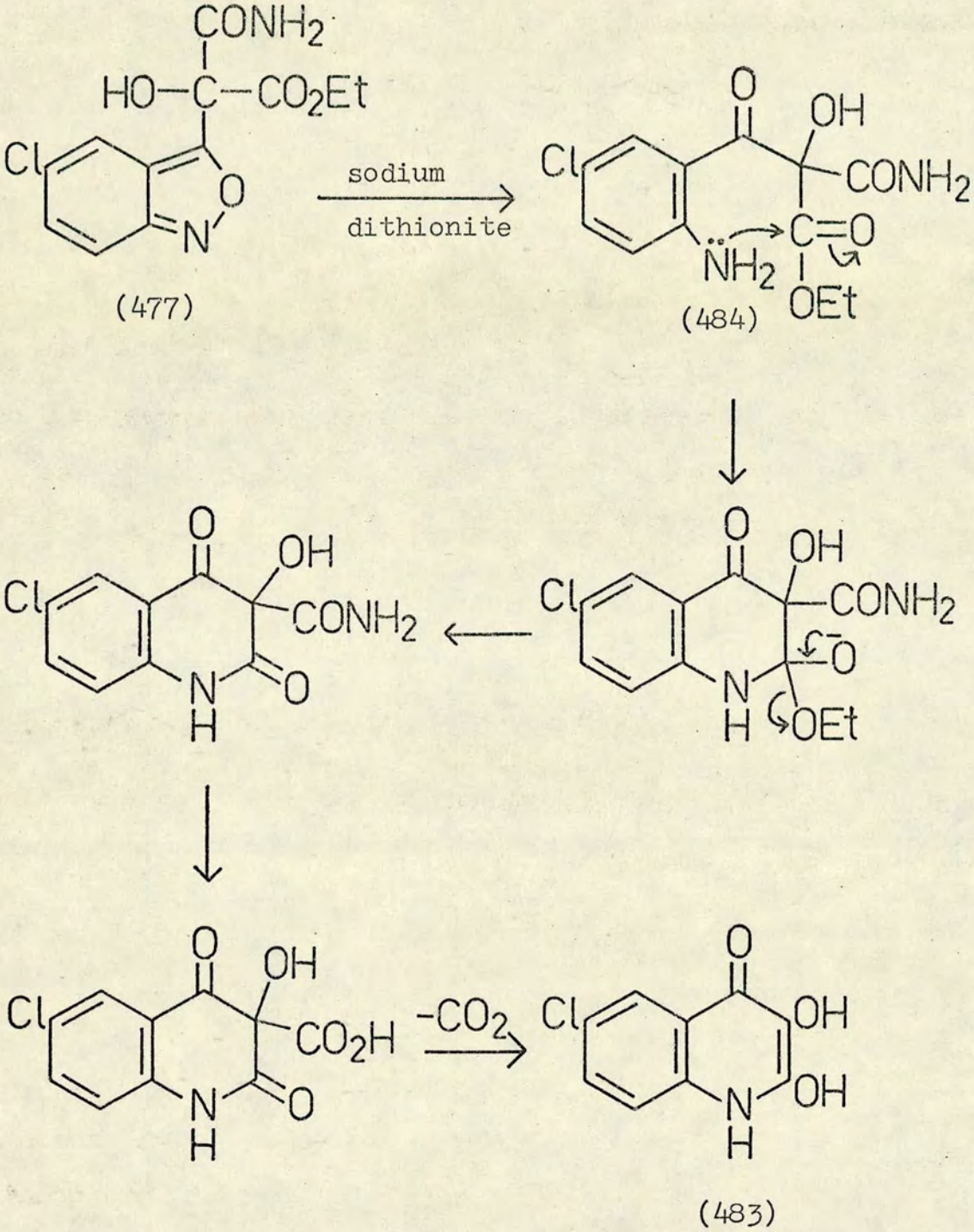
(479)

benzene-2,2'-dicarboxylic acid (479) thus establishing the position of the chlorine atom. This result has analogy in

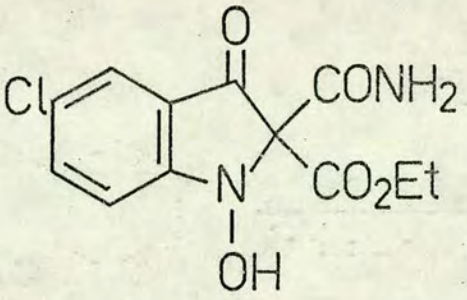


(480) (481)

the known[179] oxidation of anthranil (480) to azoxybenzene-2,2'-dicarboxylic acid (481). The observed stability of (477) to acetylation is in accord with the normal inertness of tertiary hydroxyl groups to acetylation. This stability to acetylation excludes a possible alternative structure (482) in which the N-hydroxyl group would be readily acetylated. The attempted degradation of (477) under alkaline conditions gave a complex mixture from which no

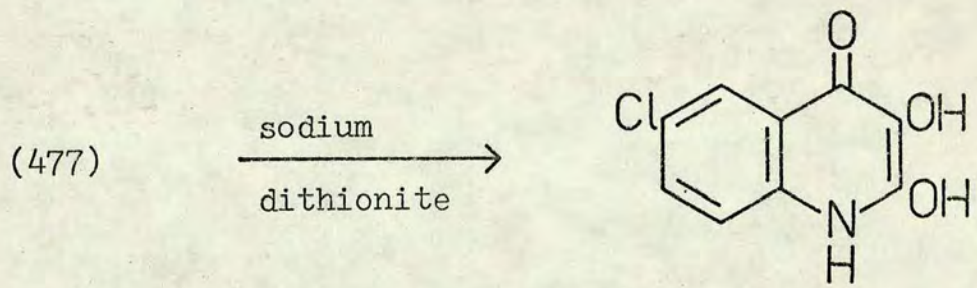

CONH2
HO—C—CO2Et
Cl
O
N
sodium
dithionite
(477)
O
OH
CONH2
Cl
NH2
C=O
OEt
(484)
O
OH
CONH2
Cl
N
H
C
O
OEt
O
OH
CONH2
Cl
N
H
O
O
OH
CO2H
Cl
N
H
O
-CO2
O
OH
OH
Cl
N
H
(483)

Scheme 83



(482)

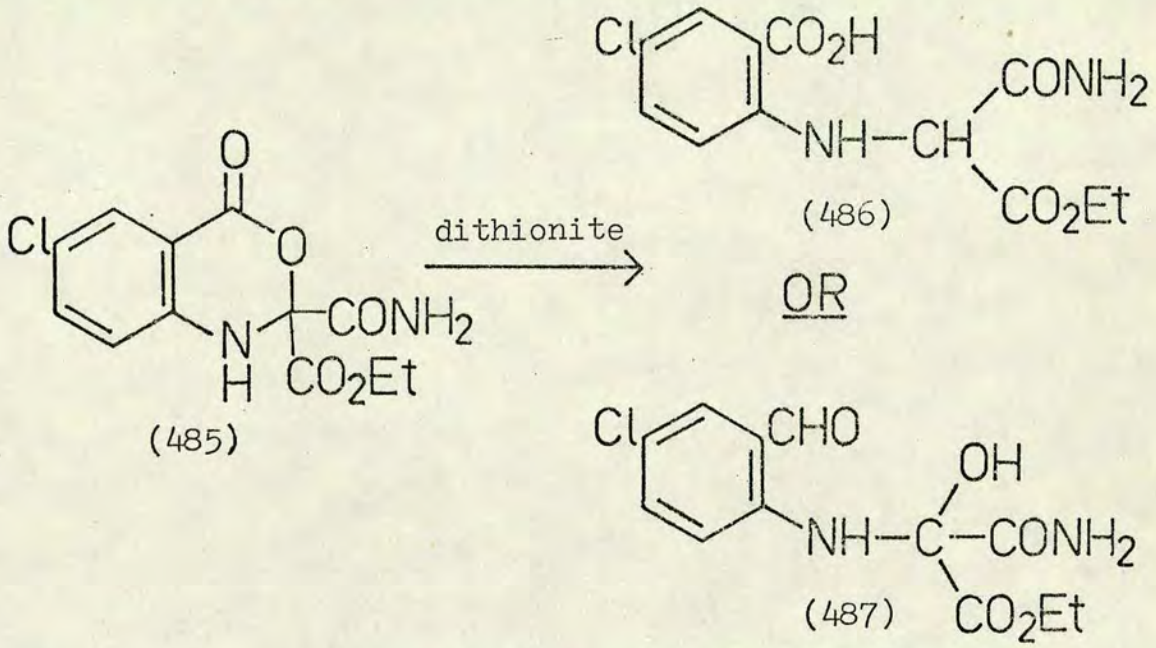
identifiable products could be isolated. However, a product whose properties are consistent with its formulation as 6-chloro-2,3-dihydroxyquinolin-4(1H)-one (483) was obtained by the sodium dithionite reduction of the anthranil (477).



(483)

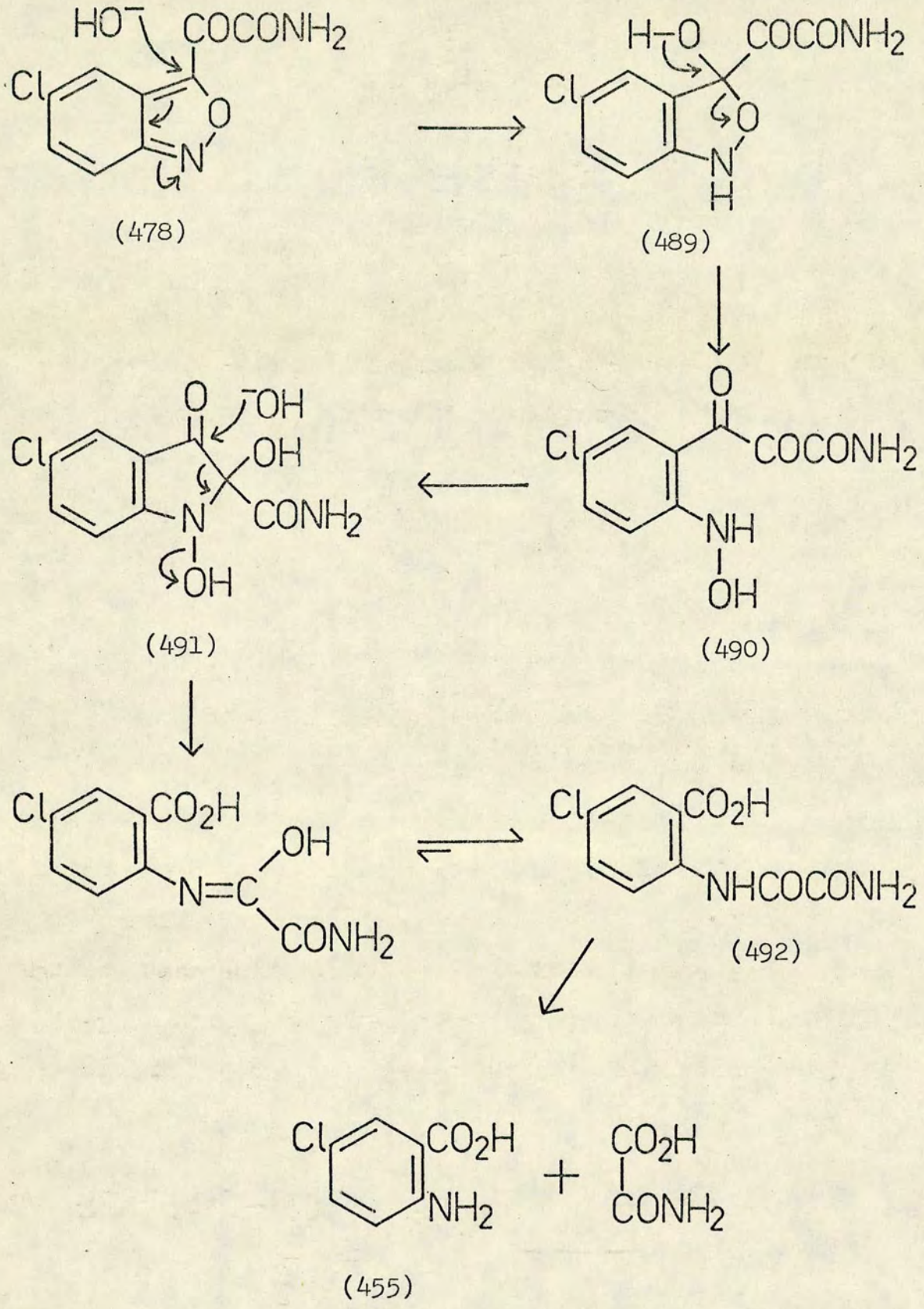
The elemental analysis and mass spectral properties were consistent with the assigned structure (483) which also accounts for the pattern of hydroxyl and carbonyl absorption in its i.r. spectrum. In addition the reduction product (483) gave a deep blue colour with iron (III) chloride characteristic[180,181] of 2,3-dihydroxyquinolin-4(1H)-ones. The formation of the 2,3-dihydroxyquinolin-4(1H)-one (483) provides support for the structure (477) and is rationalised as shown in Scheme 83. Reduction of the anthranil (477) yields[43] the amino-intermediate (484) cyclisation of which,

by an amino-ester condensation and subsequent hydrolysis and decarboxylation, affords the 2,3-dihydroxyquinolin-4(1H)-one (483). The formation of (483) eliminates the structure (485) as a possible alternative to the anthranil structure

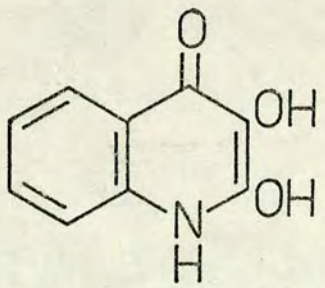


(477). Reduction of (485) would be expected to give as initial products either (486) or (487), neither of which could give rise to 6-chloro-2,3-dihydroxyquinolin-4(1H)-one (483). Examples are known (see page 37) of the removal of a 6-chloro-substituent in quinolines and quinazolines during catalytic reduction. In the hope of obtaining the known[182] compound (488) catalytic reduction of the chloroquinolinone (483) was attempted but resulted only in the recovery of starting material.

The i.r. spectrum of the product tentatively assigned the anthranil structure (478) showed absorption due to a primary amino-group and two carbonyl groups. The ^{1}H n.m.r. spectrum confirmed the presence of the amino-group and the lack of

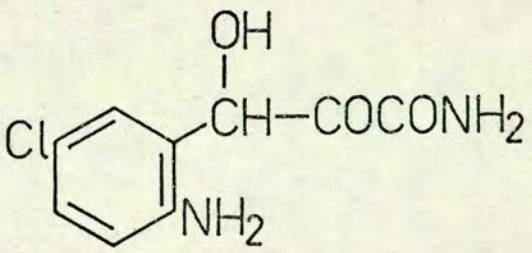

HO⁻
COCONH2
Cl
O
N
(478)
H–O
COCONH2
Cl
O
N
H
(489)
O
COCONH2
Cl
NH
OH
(490)
O
⁻OH
Cl
OH
N
CONH2
OH
(491)
Cl
CO2H
OH
N=C
CONH2
Cl
CO2H
NHCOCONH2
(492)
Cl
CO2H
NH2
+
CO2H
CONH2
(455)

Scheme 84

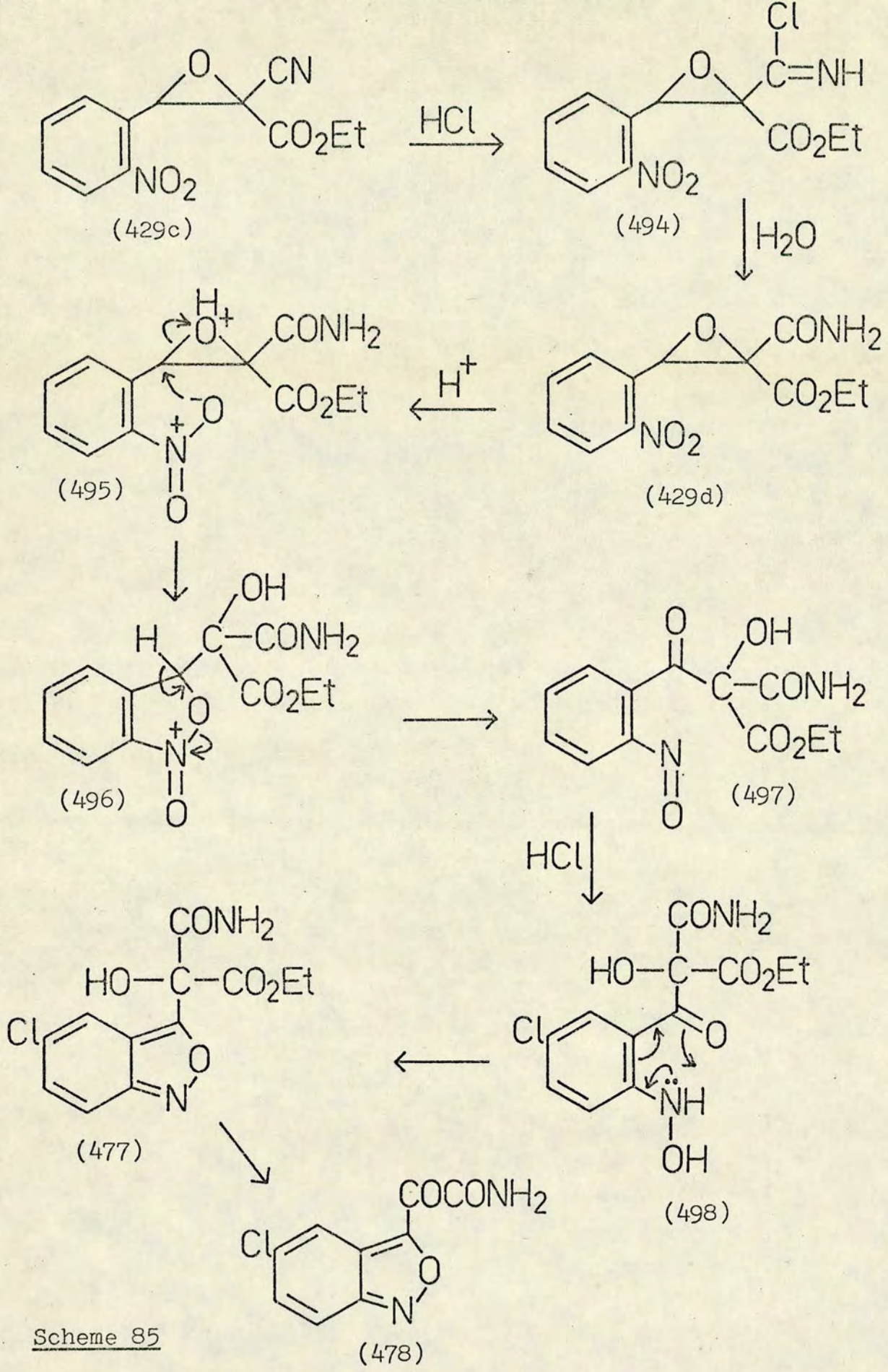


(488)

signals due to an ethyl group showed that the ester function had been lost. Reaction of the anthranil (478) with aqueous sodium hydroxide yielded 5-chloroanthranilic acid (455). This result, which confirms the position of the chlorine atom in (478), can be rationalised as shown in Scheme 84. Thus hydration of the anthranil (478) and ring-opening of the hydrate (489) leads to the hydroxylamino-intermediate (490) which recyclises to the 1-hydroxyindolinone (491). The base-catalysed ring-opening of the indolinone (491)[162] (see page 155) to the N-acylanthranilic acid (492) and subsequent hydrolysis then accounts for the formation of 5-chloroanthranilic acid (455). The sodium dithionite reduction of (478) gave a very low yield of a yellow solid whose mass spectrum indicated an uptake of four hydrogen atoms which suggests that the product has the amino-structure (493). In support of

(478) ⟶ 

(493)

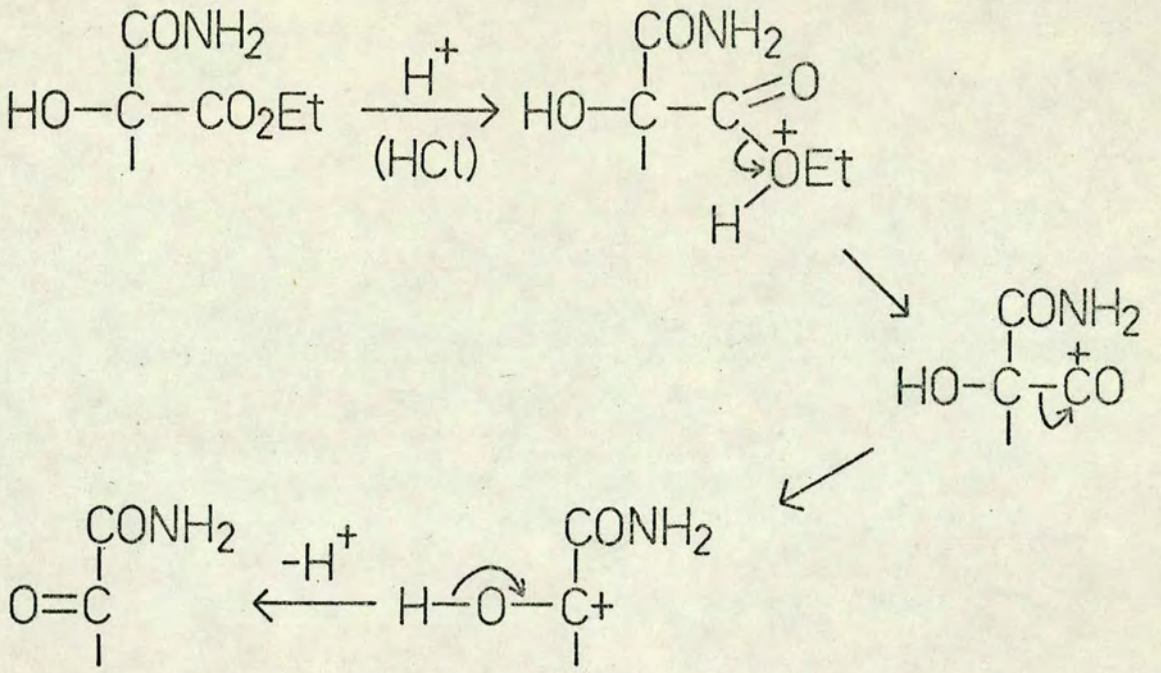


(429c) (494) (495) (429d) (496) (497) (498) (477) (478)

Scheme 85

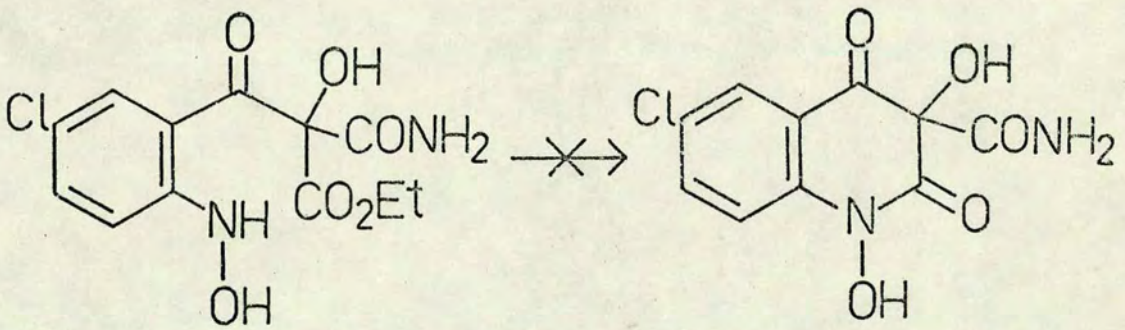
this structure the i.r. spectrum of the product showed two carbonyl absorptions and had complex absorption bands at >3000 cm^{-1} consistent with the presence of the two primary amino-groups and the hydroxyl group in (493). However there was insufficient of this product for further characterisation.

The formation of the anthranil products (477) and (478) as well as the amidoester-epoxide (429d) from the nitrile (429c) is rationalised in Scheme 85. The isolation of the epoxide (429d) in this reaction suggests that hydrolysis of the cyano-group in (429c) via the imino-chloride intermediate (494) occurs early in the reaction sequence. Participation by the nitro-group in the ring-opening of the protonated epoxide (495) and oxygen transfer lead [(495)→(496)→(497)] to the nitroso-intermediate (497). Reaction of (497) with hydrogen chloride affords (498) which cyclises by a hydroxylamino-ketone condensation giving the anthranil (477) from which loss of the elements of ethyl formate yields the anthranil (478). The latter process [(477)→(478)] is akin to the known[183] acid-catalysed conversion of α-hydroxyacids into carbonyl compounds which is believed[184] to follow a carbonium ion mechanism. A similar mechanism (Scheme 86) would account for the transformation of (477) into (478). At the hydroxylamino-stage (498) in the mechanism (Scheme 85) it should be possible for condensation through the ester group to occur but none of the corresponding chloroquinolinone (499) was detected.



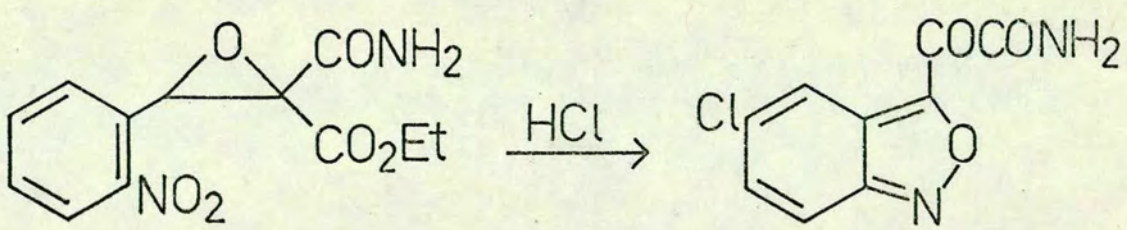
Scheme 86

The reaction of 1-carbamoyl-1-cyano-2-(2-nitrophenyl) ethylene oxide (429d) with hydrogen chloride gave a complex



(498) (499)

mixture from which only the anthranil (478) could be isolated. The formation of (478) from (429d) can be formulated as



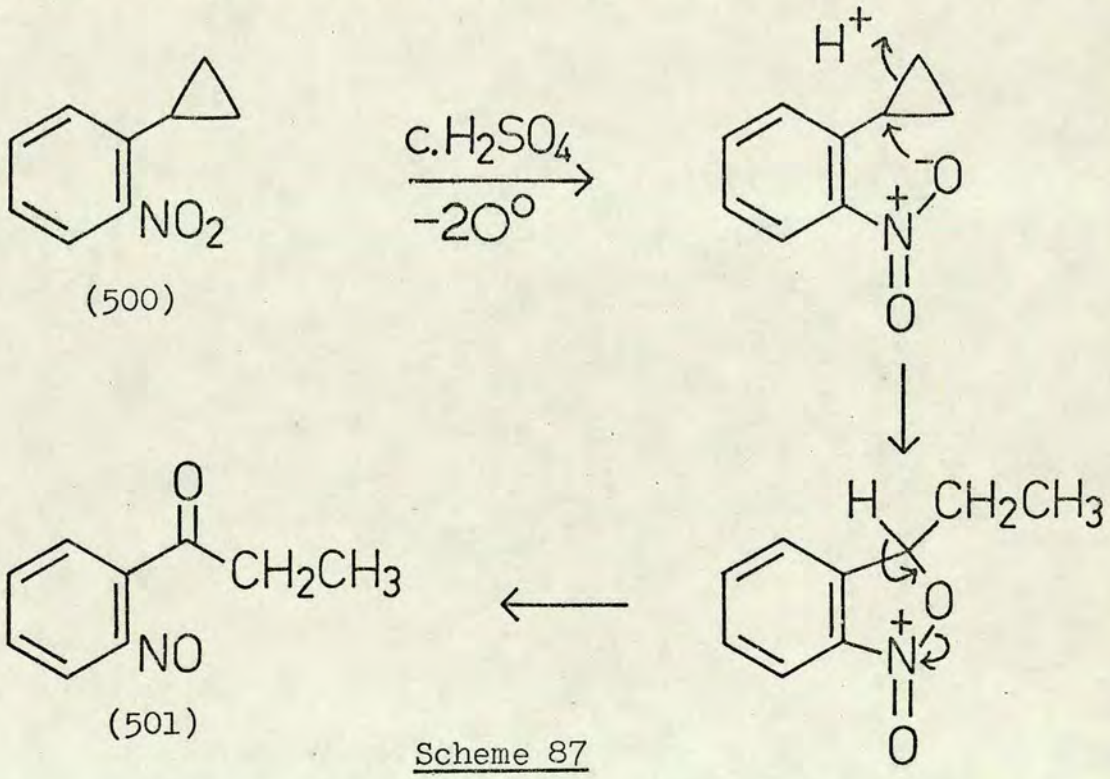
(429d) (478)

indicated by the steps [(429d)→ →(478)] in Scheme 85. The isolation of ammonium chloride in this reaction points to the formation of products resulting from the loss of the amido-group although no such products could be isolated.

In summary, an efficient route to 1,1-disubstituted 2-(2-nitrophenyl)ethylene oxides has been developed. The other initial aim of this work, namely to produce a viable synthetic route to 3-hydroxyquinolin-4(1H)-ones, has not been successfully achieved although the acid-catalysed reactions of the epoxides studied have provided a number of interesting results which demand further investigation. Cyclisation to quinolinones appears to be successful only through an acetyl or a benzoyl group, even when the molecule has the option of cyclising through benzoyl or ester and benzoyl or cyano groups. When no choice is available and only cyano and/or ester groups are present the reaction takes a different course leading to products tentatively assigned anthranil structures. In general it has been shown that there is a greater degree of participation by the nitro-group in the 1,1-diacylated 2-(2-nitrophenyl)ethylene oxides compared to their mono-substituted analogues, although this participation has not, in every case, led to increased yields of chloroquinolinones.

3.6 The Reaction of 1-Benzoyl-2-(2-nitrophenyl)cyclopropane with Hydrogen Chloride

By analogy with the behaviour of substituted 2-nitrophenylethylene oxides (see before) it might be expected that participation by the nitro-group would occur in the acid-catalysed ring-opening of other 2-nitrophenyl-substituted three-membered rings. Indeed one such analogous reaction has been reported, namely the reaction[185] of 2-nitrophenylcyclopropane (500) with concentrated sulphuric acid at low temperature to afford 2-nitrosopropiophenone (501). This interesting rearrangement is formally akin to the acid-catalysed



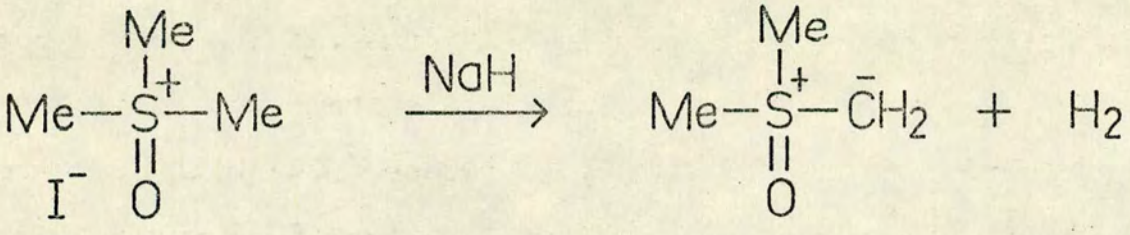
(500)

(501)

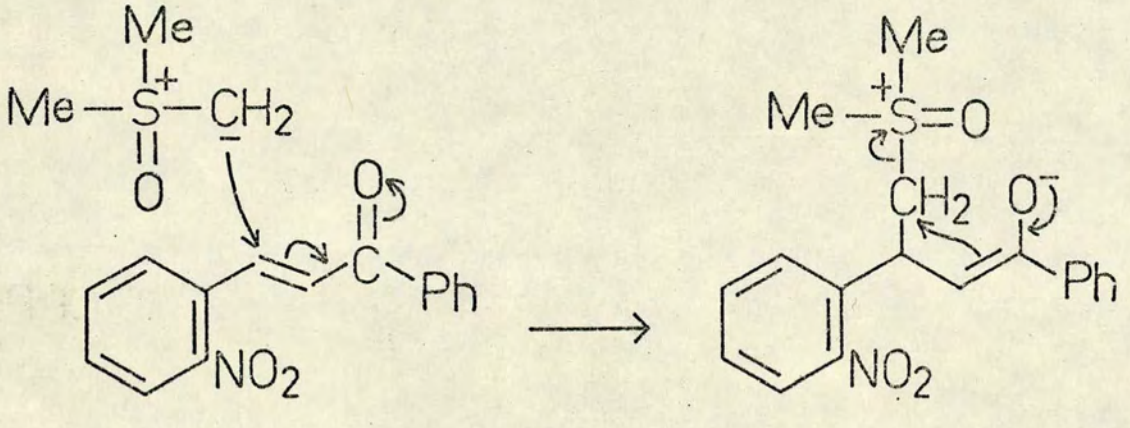
Scheme 87

conversion of 2-nitrophenylethylene oxide (363) into 2-nitrosobenzoylmethanol (366)(See Scheme 60, page 140) and can be rationalised as shown in Scheme 87.

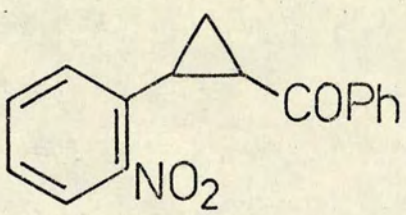
As an extension of the rearrangement [(500)→(501)] and by analogy with the transformation of cis and trans-1-



(502) (503)



(411a)

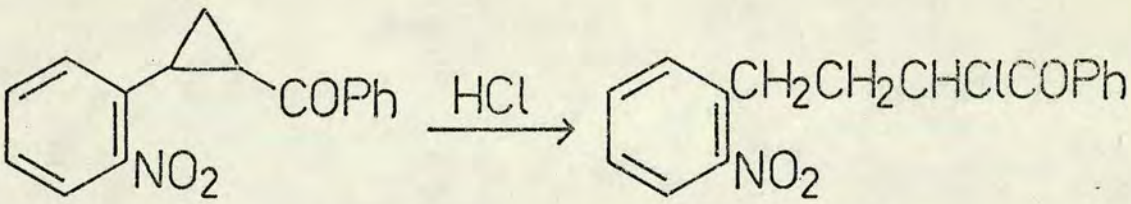


(504)

Scheme 88

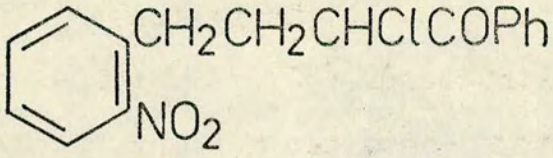
benzoyl-2-(2-nitrophenyl)ethylene oxides into 6-chloro-1, 3-dihydroxy-2-phenylquinolin-4(1H)-one (cf Scheme 62, page 143) it was decided to investigate the reaction of 1-benzoyl-2-(2-nitrophenyl)cyclopropane (504) with hydrogen chloride. The cyclopropane derivative (504) was readily prepared by treating 2-nitrobenzylideneacetophenone (411a) with dimethyloxosulphonium methylide (503) generated *in situ* from trimethyloxosulphonium iodide (502) and sodium hydride (Scheme 88).

Treatment of the cyclopropane (504) with ethereal hydrogen chloride gave a product identified as 1-benzoyl-1-chloro-3-(2-nitrophenyl)propane (505) on the basis of the

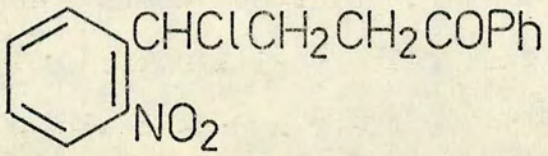


(504) (505)

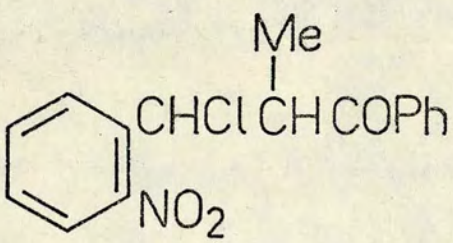
following evidence. Elemental analysis indicated the formula $C_{16}H_{14}ClNO_3$ corresponding to the addition of hydrogen chloride to the cyclopropane. However, due to the very low ion pressure a confirmatory mass spectral analysis could not be obtained for the compound. That the nitro-group had not been involved in any interaction was indicated by the i.r. spectrum which showed nitro-absorption at 1540 and 1360 cm^{-1}, as well as carbonyl-absorption at 1680 cm^{-1} due to an intact benzoyl group. Addition of hydrogen chloride to the cyclopropane ring in (504) can theoretically give rise to the six structures [(505)--(510)]. However, the ^1H n.m.r. spectrum



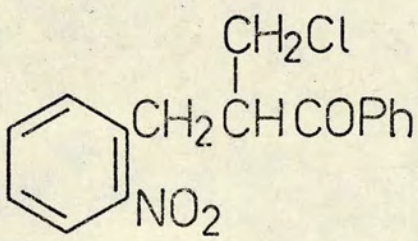
(505)



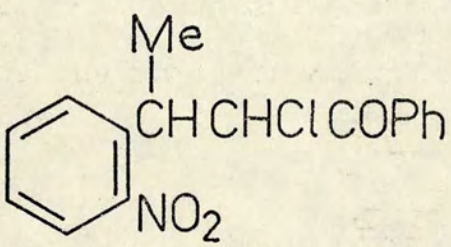
(506)



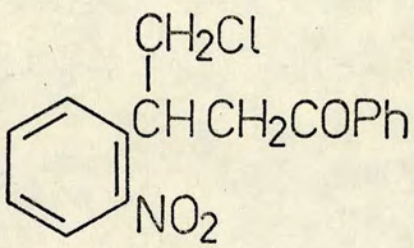
(507)



(508)



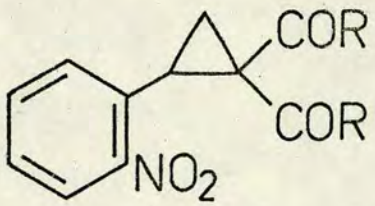
(509)



(510)

of the product showed no signals due to the protons of a methyl group thus excluding structures (507) and (509). In addition, the ^1H n.m.r. spectrum contained a signal due to a single hydrogen which was coupled to only two other protons. This feature eliminates structures (508) and (510) in which the tertiary hydrogen would be coupled to four hydrogens. The structure of the product was shown to be (505) rather than the alternative structure (506) by its ability to liberate iodine from starch-iodide solution. It has been demonstrated[145] that phenacyl halides liberate iodine from iodides in contrast to benzyl halides which are inert. In further accord with the structure (505) treatment of the hydrogen chloride adduct with ethanolic sodium ethoxide regenerated the cyclopropane (504).

No products resulting from participation by the nitro-group in the opening of the cyclopropane ring in (504) were detected. However, by analogy with the increased participation in the 1,1-diacylated 2-(2-nitrophenyl)ethylene oxides



(511)

compared to the corresponding monoacylated epoxides, such products might be formed to a greater extent in the acid-catalysed reactions of diacylated 2-nitrophenylcyclopropanes (511).

Experimental

3.7 The Attempted Epimerisation of trans-1-Aroyl-2-(2-nitrophenyl)ethylene Oxides

(For general experimental details, see Appendix)

5-Chloro-2-nitrobenzaldehyde was prepared[186] by nitrating 3-chlorobenzaldehyde, (87%), m.p. 68-72° (lit.,[186] 78°).

Preparation of Substituted 2-Nitrophenylethylene Oxides

The epoxides (400a-c) were prepared by a method based on that of Cromwell and Setterquist.[150]

A suspension of 2-nitrobenzaldehyde (7.5g, 0.05 mol) and the 4-substituted phenacyl bromide (399a-c)(0.05 mol) in methanol (150 ml) was treated at 0-12° (ice bath) with a solution of sodium (1.2g, 0.05 mol) in methanol (20.0 ml). The mixture was stirred at room temperature for 3h and was then acidified to pH 6 by the addition of glacial acetic acid. The solid was collected, washed with water and crystallised to yield the corresponding epoxides (400a-c).

Trans-1-(4-Bromobenzoyl)-2-(2-nitrophenyl)ethylene oxide (400a) formed colourless needles (86%), m.p. 173° (from dioxan), $\nu_{max.}$ 1690 (CO) and 1540 and 1350 (NO_2) cm^{-1}, τ [$CDCl_3$] 1.77 - 2.50 (8H,m,ArH), 5.41 (1H, d, J 2 Hz, CH) and 5.86 (1H, d, J 2 Hz, CH),

Found: C, 51.9; H, 2.9; N, 3.9%.

$C_{15}H_{10}BrNO_4$ requires: C, 51.7; H, 2.9; N, 4.0%.

Trans-2-(2-nitrophenyl)-1-(4-phenylbenzoyl)ethylene oxide (400b), (75%), had m.p. 156° (from aqueous dimethylformamide), $\nu_{max.}$ 1680 (CO) and 1530 and 1350 (NO_2) cm^{-1}, τ [$CDCl_3$]

1.79 - 2.64 (13H,m,ArH), 5.37 (1H, d, J 2 Hz, CH) and 5.77 (1H, d, J 2 Hz, CH),

Found: C, 72.7; H,4.1; N, 4.3%.

$C_{21}H_{15}NO_4$ requires: C, 73.0; H,4.4; N, 4.1%.

Trans-1-(4-Nitrobenzoyl)-2-(2-nitrophenyl)ethylene oxide (400c) formed yellow needles (62%), m.p. 142° (from glacial acetic acid-ethanol), $\nu_{max.}$ 1680 (CO) and 1530 and 1350 (NO_2) cm^{-1}, τ [$CDCl_3$] 1.64 - 2.52 (8H,m,ArH), 5.39 (1H, d, J 2 Hz, CH) and 5.81 (1H, d, J 2 Hz, CH),

Found: C, 57.4; H, 3.3; N, 8.7%.

$C_{15}H_{10}N_2O_6$ requires: C, 57.3; H, 3.2; N, 8.9%.

Trans-1-Benzoyl-2-(5-chloro-2-nitrophenyl)ethylene oxide (401) was prepared similarly by reacting 5-chloro-2-nitrobenzaldehyde with phenacyl bromide, (97%), m.p. 147° (from glacial acetic acid-ethanol), $\nu_{max.}$ 1690 (CO) and 1540 and 1350 (NO_2) cm^{-1}, τ [$CDCl_3$] 1.78 - 2.58 (8H,m,ArH), 5.34 (1H, d, J 2 Hz, CH) and 5.76 (1H, d, J 2 Hz, CH),

Found: C, 59.2; H, 3.3; N, 4.6%.

$C_{15}H_{10}ClNO_4$ requires: C, 59.3; H, 3.3; N, 4.6%.

Trans-1-Ethoxycarbonyl-2-(2-nitrophenyl)ethylene oxide (402)

A solution of ethyl chloroacetate (2.5g, 0.02 mol) and 2-nitrobenzaldehyde (3.0g, 0.02 mol) in absolute ethanol 20.0 ml) was treated at 0° (ice-bath)with a solution of sodium (0.46g, 0.02 mol) in absolute ethanol (20.0 ml) at such a rate that the temperature stayed between 0 and 5°. Stirring was continued in the melting ice-bath for 15h and the mixture was adjusted to pH 6 by the addition of glacial acetic acid

and was filtered to remove inorganic material. The filtrate was evaporated under reduced pressure and the resultant oil was treated with water and was extracted into chloroform to give an oil which afforded the solid product (4.5g) on treatment with ether. Recrystallisation gave the pure epoxide (402) (3.6g, 63%), m.p. 58° (from light petroleum), $\nu_{max.}$ 1725 (CO), 1530 and 1340 (NO_2) cm^{-1}, τ [$CDCl_3$] 1.82 (1H, dd, J_{ortho} 9 Hz, J_{meta} 2 Hz, ArH), 2.28 - 2.56 (3H,m,ArH), 5.35 (1H, d, J 2 Hz, CH), 5.68 (2H, q, J 7 Hz, CH_2), 6.63 (1H, d, J 2 Hz, CH) and 7.67 (3H, t, J 7 Hz, Me),

Found: C, 55.6; H, 4.7; N, 5.8%.

$C_{11}H_{11}NO_5$ requires: C, 55.7; H, 4.7; N, 5.9%.

3-Chloropentane-2,4-dione (409) was prepared[187] by the reaction of acetylacetone with sulphuryl chloride, (61%), b.p. 150-2° (lit.,[187] 154°).

The Attempted Preparation of 1,1-Diacetyl-2-(2-nitrophenyl) ethylene oxide (408a)

2-Nitrobenzaldehyde (5.3g, 0.033 mol) in methanol (50 ml) was stirred at room temperature with 3-chloropentane-2,4-dione (409)(4.5g, 0.033 mol) and anhydrous potassium carbonate (2.4g) for 1.5h by which time the initial yellow colour had darkened to brown. The methanol was evaporated under reduced pressure to give a gummy residue which was treated with water and ether. Work-up of the ether layer gave a gum whose t.l.c. in benzene-ether (1:1) over silica indicated a four component mixture containing 2-nitrobenzaldehyde. The gum was dissolved in ether and washed with saturated

aqueous sodium hydrogen sulphite (100 ml). The ether layer gave a gum (5.1g) which was chromatographed over alumina but gave no definable products.

Attempted Epimerisations

The method employed was basically that described by Cromwell and Setterquist.[150]

Trans-1-Ethoxycarbonyl-2-(2-nitrophenyl)ethylene oxide (402)

The trans-epoxide (402) (0.5g, 0.002 mol) in methanol (8.0 ml) was treated with 10% w/v methanolic sodium methoxide (0.3 ml) and the mixture was left at room temperature for 18h. The solid which had separated was collected, combined with a second crop obtained by concentrating the filtrate (total 0.4g) and identified (m.p., i.r. and ^{1}H n.m.r. spectra) as unchanged trans-epoxide (402). The reaction was repeated with stirring at 50° for 18h, and again only unreacted trans-epoxide (402) (90%) was recovered.

Trans-1-(4-Bromobenzoyl)-2-(2-nitrophenyl)ethylene oxide (400a)

(a) The attempted epimerisation of the trans-epoxide (400a) (0.7g, 0.002 mol) suspended in methanol (16.0 ml) using 10% w/v methanolic sodium methoxide (0.3 ml) as described before gave a quantitative recovery of unchanged trans-epoxide (400a) identical (m.p., i.r. and ^{1}H n.m.r. spectra) to an authentic sample.

(b) The trans-epoxide (400a)(0.7g, 0.002 mol) in dimethyl sulphoxide (16.0 ml) was stirred at room temperature with 10% w/v methanolic sodium methoxide (0.3 ml). The mixture was neutralised with glacial acetic acid and poured into water (60 ml). On scratching a cream solid (0.6 g) separated and

was identified (m.p., i.r. and ^{1}H n.m.r. spectra) as unchanged trans-epoxide (400a).

Trans-2-(2-Nitrophenyl)-1-(4-phenylbenzoyl)ethylene oxide (400b)

(a) The attempted epimerisation of the trans-epoxide (400b) as described before using methanolic sodium methoxide gave a quantitative recovery of the starting material (400b), identical (m.p., i.r. and ^{1}H n.m.r. spectra) with an authentic sample.

(b) The trans-epoxide (400b)(0.35g, 0.001 mol) in anhydrous dioxan (15.0 ml) was added to a suspension of sodium hydride (0.7g, 0.003 mol) in anhydrous dioxan (15.0 ml) and the mixture was stirred at room temperature for 15h. The reaction mixture was poured into ether (50 ml) containing glacial acetic acid (5.0 ml) with vigorous stirring and the excess of acetic acid was neutralised with aqueous N-sodium carbonate. The ether extract gave unchanged trans-epoxide (400b) (0.3g), m.p. 156°, identical (i.r. and ^{1}H n.m.r. spectra) with an authentic sample.

Trans-1-(4-Nitrobenzoyl)-2-(2-nitrophenyl)ethylene oxide (400c)

The attempted epimerisation of the trans-epoxide (400c) as described before, using methanolic sodium methoxide gave a quantitative recovery of the trans-epoxide (400c), m.p. 141°, identical (i.r. and ^{1}H n.m.r. spectra) with an authentic sample.

Trans-1-Benzoyl-2-(5-chloro-2-nitrophenyl)ethylene oxide (401)

The attempted epimerisation of the trans-epoxide (401) in methanolic sodium methoxide as described before gave unchanged trans-epoxide (401) (90%), m.p. 147°, identical (i.r. and ^{1}H n.m.r. spectra) to an authentic sample.

3.8 The Preparation of the 2-Nitrobenzylidene Derivatives of Active Methylene Compounds

Benzoylacetonitrile was prepared[188] by reacting phenacyl bromide with potassium cyanide, (57%), m.p. 79° (from ethanol-light petroleum) (lit.,[188] 82°).

2-Nitrobenzylideneacetophenone (411a) was prepared[156] by the sodium hydroxide catalysed condensation of 2-nitrobenzaldehyde with acetophenone (44%), m.p. 120° (from ethanol)(lit.,[156] 124°).

Ethyl 2-Nitrobenzylidenebenzoylacetate (411b)

A solution of 2-nitrobenzaldehyde (9g, 0.06 mol) and ethyl benzoylacetate (15.4g, 0.08 mol) in glacial acetic acid (5.0 ml) containing piperidine (6.0 ml) was left at room temperature for 24h and was then diluted with water. The resultant gummy solid was collected and washed with ether to give the product (17.3g, 89%), m.p. 106° (from ethanol) (lit.,[49] 107°), τ [$CDCl_3$] 1.69 (1H,s,CH), 1.90 - 2.79 (9H, m,ArH), 5.72 (2H, q, J 7 Hz, CH_2) and 8.88 (3H, t, J 7 Hz, Me).

2-Nitrobenzylidenebenzoylacetone (411c)

A solution of 2-nitrobenzaldehyde (3.8g, 0.025 mol) and benzoylacetone (5.4g, 0.033 mol) in glacial acetic acid (10.0 ml) containing piperidine (2.5 ml) was stirred at room temperature for 72 h and was then poured into water. The resultant oil was extracted into chloroform and the extract was washed with dilute aqueous hydrochloric acid and 10% w/v aqueous sodium hydroxide. A solid separated during the alkaline wash and was collected and acidified (dilute aqueous hydrochloric acid)

to give benzoylacetone (1.6g), identical (i.r. spectrum) with an authentic sample. The chloroform extract gave an oil which, on trituration with ether, yielded the product (2.7g, 22%), m.p. 73° (from methanol)(lit.,[189] 77°), τ [$CDCl_3$] 1.83 (1H,s,CH), 1.98 - 2.76 (9H,m,ArH) and 7.56 (3H, s,Me).

2-Nitrobenzylidenebenzoylacetonitrile (411d)

A solution of 2-nitrobenzaldehyde (3.8g, 0.025 mol) and benzoylacetonitrile (4.8g, 0.033 mol) in glacial acetic acid (15.0 ml) containing piperidine (2.5 ml) was left at room temperature for 70h and was then diluted with water. The oil produced was extracted into chloroform and the extract, after washing with dilute aqueous hydrochloric acid and 10% w/v aqueous sodium hydroxide, gave a red gum which crystallised on standing to give a yellow solid (6.0g). Recrystallisation gave the product (3.4g, 31%), m.p. 95° (from methanol), $\nu_{max.}$ 2300 (CN), 1660 (CO) and 1540 and 1350 (NO_2) cm^{-1}, τ [$(CD_3)_2CO$] 2.06 - 3.08 (9H,m,ArH) and 4.32 (1H,s,CH),

Found: C, 68.8; H, 3.6; N, 10.1%.

$C_{16}H_{10}N_2O_3$ requires: C, 69.1; H, 3.6; N, 10.1%.

The solid (0.6g) which separated from the crystallisation mother liquors was chromatographed in toluene-ether (9:1) over alumina to afford the benzylidene product (411d) (0.15g) identical (m.p. and i.r. spectrum) with the sample prepared before. Further elution with toluene-ether (3:2) gave a gum (0.24g) from which no solid could be obtained.

In a repeat preparation of the benzylidene derivative (411d) the product was purified by chromatography over alumina,

rather than by crystallisation, with only a slight increase in the yield (36%).

2-Nitrobenzylidenedibenzoylmethane (411e)

A solution of 2-nitrobenzaldehyde (7.5g, 0.05 mol) and dibenzoylmethane (15.0g, 0.067 mol) in glacial acetic acid (20.0 ml) containing piperidine (5.0 ml) was stirred at room temperature for 48h. The reaction mixture was diluted with water and the product was collected, washed with water and crystallised to give the benzylidene compound (411e) (12.5g, 71%), m.p. 137° (from ethanol) (lit.,[5] 137°).

2-Nitrobenzylidenedeoxybenzoin (411f) was prepared[157] by the hydrogen chloride catalysed condensation of 2-nitrobenzaldehyde with deoxybenzoin (39%), m.p. 119° (from ethanol) (lit.,[157] 118°).

2-Nitrobenzylidenepropiophenone (411g)

A solution of 2-nitrobenzaldehyde (3.0g, 0.02 mol) and propiophenone (2.7g, 0.02 mol) in ether (100 ml) was saturated with anhydrous hydrogen chloride and the mixture was left at room temperature for 44h. The ether was evaporated under reduced pressure to yield a red gum whose t.l.c. in benzene over silica indicated the presence of both starting materials plus a third component. Chromatography of the gum in light petroleum-toluene (3:1) over alumina gave propiophenone (2.1g). Further elution with the same solvent afforded a gum (1.3g) whose t.l.c. in benzene over silica showed the presence of 2-nitrobenzaldehyde and one other component. Trituration of the gum with methanol-ether gave colourless crystals of the benzylidene product (411g) (0.4g, 10%), m.p. 80° (from ethanol)

(lit.,[5] 81°), τ [$CDCl_3$] 1.80 - 2.59 (m,ArH + CH), 7.99 (s,Me) and 8.00 (s,Me).

Diethyl 2-Nitrobenzylidenemalonate (413a) was prepared by the method described by Loudon and Wellings[4] with the modification that unreacted 2-nitrobenzaldehyde was removed from the crude product by steam distillation, (40%), m.p. 50° (from ethanol) (lit.,[4] 53°).

Ethyl 2-Nitrobenzylideneacetoacetate (413b)

A solution of 2-nitrobenzaldehyde (3.8g, 0.025 mol) and ethyl acetoacetate (4.3g, 0.033 mol) in glacial acetic acid (7.0 ml) containing piperidine (2.5 ml) was left at room temperature for 70h. The mixture was diluted with water giving an oil which was extracted into chloroform. The extract was washed with dilute aqueous hydrochloric acid and 10% w/v aqueous sodium hydroxide, and evaporated to give the benzylidene derivative (413b) as a red oil (5.1g, 49%) (lit.,[43] solid m.p. 69°), $\nu_{max.}$ 1720, 1700 (CO) and 1540 and 1350 (NO_2) cm^{-1}, τ [$CDCl_3$] 1.70 - 2.61 (m,ArH + CH), 5.66 (q, J 7 Hz, CH_2), 5.93 (q, J 7 Hz, CH_2), 7.53 (s,Me), 7.80 (s,Me), 8.64 (t, J 7 Hz, Me) and 9.02 (t, J 7 Hz, Me) which was used without further purification.

Ethyl 2-Nitrobenzylidenecyanoacetate (413c) was prepared[158] by the sodium ethoxide catalysed condensation of 2-nitrobenzaldehyde with ethyl cyanoacetate (80%), m.p. 95° (from ethanol) (lit.,[158] 96°).

2-Nitrobenzylideneacetylacetone (415a)

A solution of 2-nitrobenzaldehyde (7.5g, 0.05 mol) and

acetylacetone (6.7g, 0.067 mol) in glacial acetic acid (4.0 ml) containing piperidine (5.0 ml) was stirred at room temperature for 2h. The semi-solid reaction mixture was poured into water and the product was collected, washed with water and crystallised to give the benzylidene product (415a) (81%), m.p. 73° (from ethanol) (lit.,[49] 76°), τ [$CDCl_3$] 1.75-2.58 (5H,m,ArH + CH), 7.54 (3H,s,Me), and 7.90 (3H,s,Me).

2-Nitrobenzylidenephenylacetonitrile (415b) was prepared[160] by the sodium methoxide catalysed condensation of 2-nitrobenzaldehyde with phenylacetonitrile (64%), m.p. 128° (from ethanol) (lit.,[160] 128°). When the methanolic reaction mother liquors were evaporated and the residual gum was warmed with chloroform to achieve solution an exothermic reaction occurred. The chloroform solution was concentrated and the insoluble solid (1.5g) was collected and acidified (dilute aqueous hydrochloric acid). The i.r. spectrum of the resulting solid [$\nu_{max.}$ 3200br (NH), 2600br (OH), 1760, 1680, 1640 (CO) and 1600 (NH def.) cm^{-1}] was consistent with a mixture of 2-benzamidobenzoic acid (416) and its internal anhydride (417). This mixture was treated with the minimum volume (ca. 4 ml) of 10% w/v aqueous sodium hydroxide necessary to achieve solution. Re-acidification (dilute aqueous hydrochloric acid) gave 2-benzamidobenzoic acid (416) (1.1g) m.p. 182° (from ethanol-water), identified by comparison (m.p. and i.r. spectrum) with an authentic sample.[190]

2-Nitrobenzylidenecyanoacetamide (415c) was prepared[159] in quantitative yield by the diethylamine catalysed condensation of 2-nitrobenzaldehyde with cyanoacetamide, m.p. 172° (lit.,[159] 172°).

2-Nitrobenzylidenemalonamide (415d)

(a) The reaction of 2-nitrobenzaldehyde with malonamide in piperidine-glacial acetic acid using the conditions described for the synthesis of 2-nitrobenzylidenedibenzoylmethane (411e) resulted in an 80% recovery of 2-nitrobenzaldehyde. No product was isolated.

(b) The attempted sodium ethoxide catalysed condensation of 2-nitrobenzaldehyde with malonamide using the conditions described for the preparation of 2-nitrobenzylidenecyanoacetate (413c) again resulted only in recovery of unreacted 2-nitrobenzaldehyde (85%) and no benzylidene product (415d) was detected.

(c) 2-Nitrobenzaldehyde (3g, 0.02 mol) and malonamide (2g, 0.02 mol) were ground together and were suspended in 66% v/v aqueous ethanol (120 ml). 10% w/v Aqueous potassium hydroxide (1.0 ml) was added and the mixture was shaken at room temperature for 14h. The solvent was evaporated under reduced pressure, the residue was treated with water and the insoluble benzylidene derivative (415d) was collected (2.1g, 43%) and was shown by t.l.c. in both benzene and benzene-ether (5:1) over silica to be pure. It had $\nu_{max.}$ 3450, 3200 (NH_2), 1690, 1670 (CO), 1530 and 1350 (NO_2) cm^{-1}, M^+ 235 (M 235), but melting started at 40-43° and was not complete until 131-135°. Attempted crystallisation from ethanol and

ethyl acetate resulted only in the isolation of malonamide identified by comparison (i.r. spectrum) with an authentic sample.

2-Nitrobenzylidenemalononitrile (415e) was prepared[159] by reacting 2-nitrobenzaldehyde with malononitrile, m.p. 138° (from ethanol) (lit.,[159] 138°).

4-Nitrobenzylidenephenylacetonitrile (444) (67%) was prepared by the method employed for the 2-nitro-isomer (415b). It had m.p. 121° (from ethanol) (lit.,[191] 122°).

The Attempted Preparation of 5-Chloro-2-nitrobenzylidene-phenylacetonitrile (451)

A solution of 5-chloro-2-nitrobenzaldehyde (4.6g, 0.025 mol) and phenylacetonitrile (2.9g, 0.025 mol) in methanol (20.0 ml) was treated with a solution of sodium (0.5g, 0.2 mol) in methanol (10.0 ml). The reaction mixture was heated for 5 min at 100° and was then stirred at room temperature for 48h. The insoluble solid was collected and crystallised to yield 2-benzamido-5-chlorobenzoic acid (451) (2.6g) m.p. 256° (from ethanol) (lit.,[146] 249°), identical (i.r. spectrum) to an authentic sample.[145]

3.9 The Epoxidation of the 2-Nitrobenzylidene Derivatives of Active Methylene Compounds

1-Benzoyl-2-(2-nitrophenyl)ethylene oxide (428a)

A solution of 2-nitrobenzylideneacetophenone (411a) (0.6g, 0.0025 mol) in pyridine (8.0 ml) was treated with aqueous sodium hypochlorite (6.0 ml) and the reaction mixture was stirred at room temperature for 10 min. The mixture was diluted with water (50 ml) and was extracted with chloroform. The extract was washed with dilute aqueous hydrochloric acid (50 ml) and was evaporated to give the crude product which was crystallised to yield trans-1-benzoyl-2-(2-nitrophenyl)-ethylene oxide (428a) (0.4g, 63%), m.p. 116° (from ethanol) (lit.,[145] 118°), τ [$CDCl_3$] 1.72-2.68 (9H,m,ArH), 5.37 (1H, d, J 2 Hz, CH) and 5.79 (1H, d, J 2 Hz, CH).

1-Benzoyl-1-ethoxycarbonyl-2-(2-nitrophenyl)ethylene oxide (428b) Ethyl 2-nitrobenzylidenebenzoylacetate (411b) (0.8g, 0.0025 mol) in pyridine (4.0 ml) was reacted with aqueous sodium hypochlorite (6.0 ml) for 10 min at room temperature and was worked up as described before to give the product (428b) as a red oil (0.7g, 80%), $\nu_{max.}$ 1740, 1690 (CO) and 1540 and 1350 (NO_2) cm^{-1}, τ [$CDCl_3$] 1.77-2.75 (m,ArH), 4.70 (s,CH), 4.89 (s,CH), 5.70 (q, J 7 Hz, CH_2), 6.11 (q, J 7 Hz, CH_2), 8.81 (t, J 7 Hz, Me) and 9.21 (t, J 7 Hz, Me), M^+341 (M 341), which was used without further purification.

1-Benzoyl-1-cyano-2-(2-nitrophenyl)ethylene oxide (428d)

2-Nitrobenzylidenebenzoylacetonitrile (411d) in pyridine (4.0 ml) was stirred for 5 min at room temperature with

aqueous sodium hypochlorite (6.0 ml) and was worked up as described before to afford colourless needles of the epoxide (428d) (0.4g, 57%), m.p. 91° (from ethanol-light petroleum), $\nu_{max.}$ 1680 (CO) and 1540 and 1360 (NO_2) cm^{-1}, τ [$CDCl_3$] 1.62 - 2.58 (9H,m,ArH) and 5.04 (1H,s,CH),

Found: C, 65.8; H, 3.6; N, 9.7%.

$C_{16}H_{10}N_2O_4$ requires: C, 65.3; H, 3.4; N, 9.5%.

1,1-Dibenzoyl-2-(2-nitrophenyl)ethylene oxide (428e)

(a) The benzylidene compound (411e) (1.1g, 0.003 mol) dissolved in methylene chloride (20 ml) was treated at 0° with a solution of 3-chloroperbenzoic acid (0.7g, 0.0045 mol) in methylene chloride (15 ml) and the reaction mixture was stirred at 5° for 15h. The solution was washed with aqueous N--sodium sulphite (20 ml) and aqueous N-sodium carbonate (20 ml) and was evaporated to give starting material (0.8g), identical (m.p. and i.r. spectrum) with an authentic sample.

(b) A suspension of 2-nitrobenzylidenedibenzoylmethane (411e) (1.4g, 0.004 mol) in methanol (50 ml) was treated with potassium hydrogen carbonate (0.5g) and 30% aqueous hydrogen peroxide (0.6ml) and the mixture was stirred at room temperature for 12h. The insoluble solid (0.5g) was collected and identified (m.p. and i.r. spectrum) as the unreacted benzylidene compound (411e). The filtrate was diluted with water and was extracted into chloroform to give a gum (0.5g) from which no identifiable material could be obtained.

(c) The benzylidene compound (411e) (0.7g, 0.002 mol) in ethanol (20 ml) was stirred at 70° for 2h with 30% aqueous hydrogen peroxide (3.0 ml) and trisodium phosphate decahydrate

(0.15g). The cooled reaction mixture was filtered to give starting material (0.3g), identical (m.p. and i.r. spectrum) with an authentic sample. Colourless needles of dibenzoylmethane (0.1g) separated from the mother liquors and were collected and identified by comparison (m.p. and i.r. spectrum) with an authentic sample. No further material was obtained from the mother liquors.

(d) The benzylidene compound (411e) (7.1g, 0.02 mol) dissolved in pyridine (35.0 ml) was treated with aqueous sodium hypochlorite (45.0 ml). The reaction mixture was stirred at room temperature for 10 min and was then diluted with water (100 ml). The precipitated solid was collected and crystallised to give 1,1-dibenzoyl-2-(2-nitrophenyl)ethylene oxide (428e) (83%), m.p. 141° (from glacial acetic acid), $\nu_{max.}$ 1680 (CO), 1530 and 1350 (NO_2) cm^{-1}, τ [$CDCl_3$] 1.84 - 2.80 (19H,m,ArH) and 4.70 (1H,s,CH).

Found:	C,70.8;	H, 4.1;	N, 3.8%;	M^+ 373.
$C_{22}H_{15}NO_5$ requires:	C,70.8;	C, 4.0;	N, 3.8%;	M 373.

The Attempted Preparation of 1-Acetyl-1-benzoyl-2-(2-nitrophenyl)ethylene oxide (428c)

2-Nitrobenzylidenebenzoylacetone (411c) (0.7g, 0.0025 mol) dissolved in pyridine (4.0 ml) was reacted with aqueous sodium hypochlorite (6.0 ml) at room temperature for 2 min. The reaction mixture was diluted with water and the gummy solid was collected and triturated with ether to give a sand coloured solid which was crystallised to afford cis-1-benzoyl-2-(2-nitrophenyl)ethylene oxide (380) (0.2g), m.p. 176° (lit.,[145] 176°), identical (m.p. and i.r. spectrum) with an authentic

sample.[145] Evaporation of the ether filtrate gave a gum whose ^{1}H n.m.r. spectrum {τ [$CDCl_3$] 1.83 (s,CH), 1.86 - 2.84 (m,ArH), 4.89 (s,CH), 5.37 (d, J 2 Hz, CH), 5.79 (d, J 2 Hz, CH), 7.56 (s,Me) and 7.61 (s,Me)} indicated it to be a mixture consisting of the benzylidene starting material together with minor amounts of trans-1-benzoyl-2-(2-nitrophenyl) ethylene oxide (367) and the desired product 1-acetyl-1-benzoyl-2-(2-nitrophenyl)ethylene oxide (428c). Repetition of the reaction using dioxan as the solvent gave the same result.

The Attempted Preparation of 1-Benzoyl-2-(2-nitrophenyl)-1-phenylethylene oxide (428f)

2-Nitrobenzylidenedeoxybenzoin (411f) (0.8g, 0.0025 mol) dissolved in pyridine (4.0 ml) was reacted with aqueous sodium hypochlorite (6.0 ml) and the mixture was stirred at room temperature for 10 min or 1h. Dilution with water and filtration gave the starting material (411f) (0.7g) identified by comparison (i.r. spectrum) with an authentic sample.

Repetition of the reaction at 60° for 3h or at 100° for 3h and the mixture worked up as before gave essentially quantitative recovery of the starting material.

The Attempted Preparation of 1-Benzoyl-1-methyl-2-(2-nitrophenyl)ethylene oxide (428g)

2-Nitrobenzylidenepropiophenone (411g) (0.7g, 0.0025 mol) in pyridine (4.0 ml) was stirred at room temperature for 10 min with aqueous sodium hypochlorite (6.0 ml). The mixture was diluted with water and filtered to give unreacted starting

material (411g) (0.6g) identical (m.p. and i.r. spectrum) with an authentic sample. The reaction was repeated with stirring at room temperature for 2h. Dilution with water and filtration gave the starting material (0.3g) (identical i.r. spectrum). The aqueous filtrate was extracted with chloroform and was washed with dilute aqueous hydrochloric acid to give a gum (0.1g) whose ^{1}H n.m.r. spectrum {τ [$CDCl_3$] 1.72 - 2.60 (m,ArH), 5.40 (s,CH), 7.99 (s,Me) and 8.64 (s,Me)} indicated an approximately 60:40 mixture of the benzylidene starting material (411g) and the expected epoxide (428g).

1,1-Diethoxycarbonyl-2-(2-nitrophenyl)ethylene oxide (429a)

Diethyl 2-nitrobenzylidenemalonate (413a) (0.7g, 0.0025 mol) dissolved in pyridine (4.0 ml) was reacted with aqueous sodium hypochlorite (6.0 ml) at room temperature for 10 min. The reaction mixture was diluted with water and was extracted with chloroform. The extract was washed with dilute aqueous hydrochloric acid and evaporated to give the product as an oil (0.5g, 69%), $\nu_{max.}$ 1740 (CO), 1540 and 1350 (NO_2) cm^{-1}, τ [$CDCl_3$] 1.73 - 2.49 (4H,m,ArH), 4.91 (1H,s,CH), 5.64 (2H, q, J 7 Hz, CH_2),6.05 (2H, q, J 7 Hz, CH_2), 8.66 (3H, t, J 7 Hz, Me) and 9.13 (3H, t J 7 Hz, Me), M^+309 (M 309), which was used without further purification.

1-Cyano-1-ethoxycarbonyl-2-(2-nitrophenyl)ethylene oxide (429c)

(a) Ethyl 2-nitrobenzylidenecyanoacetate (413c) (0.6g, 0.0025 mol) in pyridine (4.0 ml) was stirred at room temperature for 2 min with aqueous sodium hypochlorite (6.0 ml) and was worked up as described above to give an oil which crystallised to yield the epoxide (429c) (0.4g, 62%), m.p. 62°

(from ethanol-light petroleum), $\nu_{max.}$ 1750 (CO) and 1530 and 1350 (NO_2) cm^{-1}, τ [$CDCl_3$] 1.70 (1H, dd, J_{ortho} 9 Hz, J_{meta} 2 Hz, ArH), 2.26 (3H,m,ArH), 5.00 (1H,s,CH), 5.56 (2H, q, J 7 Hz, CH_2) and 8.60 (3H, t, J 7 Hz, Me),

Found: C, 55.2; H, 3.9; N, 10.7%.

$C_{12}H_{10}N_2O_5$ requires: C, 55.0; H, 3.8; N, 10.7%.

(b) The benzylidene compound (413c) (0.6g, 0.0025 mol) dissolved in dioxan (8.0 ml) was stirred at room temperature for 5 min with aqueous sodium hypochlorite (6.0 ml). The mixture was diluted with water and was extracted with chloroform to give an oil which solidified on cooling to yield 1-cyano-1-ethoxycarbonyl-2-(2-nitrophenyl)ethylene oxide (429c) (0.44g, 68%) identical (m.p. and i.r. spectrum) to the sample already prepared.

1-Carbamoyl-1-ethoxycarbonyl-2-(2-nitrophenyl)ethylene oxide (429d) was prepared[167] by reacting ethyl 2-nitrobenzylidenecyanoacetate (413c) with 30% aqueous hydrogen peroxide and trisodium phosphate decahydrate (73%), m.p. 144° (from ethanol) (lit.,[167] 145°).

The Attempted Preparation of 1-Acetyl-1-ethoxycarbonyl-2-(2-nitrophenyl)ethylene oxide (429b)

Ethyl 2-nitrobenzylideneacetoacetate (413b) (0.6g, 0.0025 mol) dissolved in pyridine (4.0 ml) was stirred with aqueous sodium hypochlorite (6.0 ml) at room temperature for 5 min. The mixture was diluted with water and was then extracted with chloroform. The extract was washed with dilute aqueous hydrochloric acid and was evaporated to give the benzylidene

starting material (413b) (0.4g) which was identified by comparison of its i.r. spectrum with that of an authentic sample.

Repetition of the reaction in dioxan as solvent and stirring for 10 min again gave only the unreacted starting material (80% recovery).

1-Cyano-2-(2-nitrophenyl)-1-phenylethylene oxide (430b)

2-Nitrobenzylidenephenylacetonitrile (415b) (5.1g, 0.02 mol) dissolved in pyridine (35.0 ml) was reacted at room temperature for 10 min with aqueous sodium hypochlorite (45.0 ml). The mixture was diluted with water and filtered to afford 1-cyano-2-(2-nitrophenyl)-1-phenylethylene oxide (430b) (5.1g, 95%), m.p. 124° (from ethanol), $\nu_{max.}$ 1540 and 1360 (NO_2) cm^{-1}, τ [$CDCl_3$] 1.71 (1H, dd, J_{ortho} 9 Hz, J_{meta} 2 Hz, ArH), 2.38 (8H,m,ArH) and 5.30 (1H,s,CH), m/e (rel. intensity, %) 250 (12), 135 (100), 131 (22), 119 (51) and 115 (45),(M 266),

Found: C, 67.4; H, 3.8; N, 10.9%.

$C_{15}H_{10}N_2O_3$ requires: C, 67.7; H, 3.8; N, 10.5%.

1-Carbamoyl-1-cyano-2-(2-nitrophenyl)ethylene oxide (430c)

(a) 2-Nitrobenzylidenecyanoacetamide (415c) (0.5g, 0.0025 mol) dissolved in pyridine (4.0 ml) was reacted with aqueous sodium hypochlorite (6.0 ml) for 10 min at room temperature and was then diluted with water. The mixture was extracted with chloroform, the extract was washed with dilute aqueous hydrochloric acid and was evaporated to give 1-carbamoyl-1-cyano-2-(2-nitrophenyl)ethylene oxide (430c) (0.1g, 23%).

(b) The benzylidene compound (415c) (0.5g, 0.0025 mol) dissolved in dioxan (10.0 ml) was stirred at room temperature

for 18h with aqueous sodium hypochlorite (6.0 ml). The mixture was diluted with water and extracted with chloroform to give the epoxide (430c) (0.2g, 29%), m.p. 166° (decomp.) (from ethanol), $\nu_{max.}$ 3450, 3300 (NH_2), 1680 (CO), and 1540 and 1350 (NO_2) cm^{-1}, τ [$(CD_3)_2CO$] 1.66 (1H, dd, J_{ortho} 9 Hz, J_{meta} 2 Hz, ArH), 2.18 (3H,m,ArH) and 4.82 (1H,s,CH),

Found: C, 51.2; H, 3.0; N, 18.0%; M^+ 236.

$C_{10}H_7N_3O_4$ requires: C, 51.5; H, 3.0; N, 18.0%; M+3 236.

Acidification of the alkaline aqueous phase with dilute aqueous hydrochloric acid precipitated 1-(N-chlorocarbamoyl)-1-cyano-2-(2-nitrophenyl)ethylene oxide (441) (0.4g), m.p. 147° (from ethyl acetate-light petroleum), $\nu_{max.}$ 3200 (NH), 1700 (CO), and 1540 and 1360 (NO_2) cm^{-1},

Found: C, 45.4; H, 2.3; N, 16.0%.

$C_{10}H_6ClN_3O_4$ requires: C, 44.9; H, 2.2; N, 15.7%.

The N-chloroamide (441) dissolved in saturated aqueous sodium hydrogen carbonate and was regenerated on acidification (dilute aqueous hydrochloric acid). It gave a positive Lassaigne test for chlorine but failed to give a precipitate of silver chloride when its solution in acetonitrile was treated with silver nitrate in acetonitrile. Crystallisation of the N-chloroamide from ethanol converted it into the epoxide (430c).

The Attempted Preparation of 1,1-Dicarbamoyl-2-(2-nitrophenyl)ethylene Oxide (430d)

(a) A suspension of 2-nitrobenzylidenemalonamide (415d) (0.7g, 0.003 mol) in dioxan (20.0 ml) was stirred at room temperature

for 1 min with aqueous sodium hypochlorite (5.0 ml) by which time all of the solid had dissolved and an oil had separated. The mixture was diluted with water and extracted with chloroform to afford an oil which solidified on cooling to give 2-nitrobenzaldehyde (0.4g), identified by comparison (i.r. spectrum) with an authentic sample.

(b) The benzylidene compound (415d) (1.0g, 0.004 mol) suspended in 85% v/v aqueous dioxan (40.0 ml) was acidified with aqueous 2N-sulphuric acid (4 drops). Aqueous 1.5N-sodium hypochlorite (8.0 ml) was added dropwise with stirring, keeping the pH slightly less than 7 by the addition of aqueous 2N-sulphuric acid. Stirring was continued for 0.5h at room temperature and the mixture was then diluted with water and extracted with chloroform to yield 2-nitrobenzaldehyde (0.3g) identical (i.r. spectrum) with an authentic sample.

The Attempted Preparation of 1,1-Dicyano-2-(2-nitrophenyl) ethylene oxide (430e)

2-Nitrobenzylidenemalononitrile (415e) (0.5g, 0.0025 mol) dissolved in pyridine (4.0 ml) was stirred at room temperature for 10 min with aqueous sodium hypochlorite (6.0 ml). The mixture was diluted with water and extracted with chloroform to give (after washing with dilute aqueous hydrochloric acid) a gummy solid, trituration of which with methanol-ether afforded 1-carbamoyl-1-cyano-2-(2-nitrophenyl)ethylene oxide (430c) (0.15g) m.p. 165° (decomp.) (from ethanol), identified by comparison (m.p. and i.r. spectrum) with a sample prepared previously. T.l.c. of the mother liquors in ether over silica showed them to contain an inseparable mixture of

starting benzylidene compound (415e) and epoxide (430e).

The Attempted Preparation of 1,1-Diacetyl-2-(2-nitrophenyl) ethylene Oxide (430a)

(a) A mixture of 2-nitrobenzylideneacetylacetone (415a) (2.3g, 0.01 mol), 30% aqueous hydrogen peroxide (15.0 ml), trisodium phosphate decahydrate (0.7g) and ethanol (15.0 ml) was stirred at 70° for 2h on a water bath. The cooled reaction mixture was extracted into chloroform to give a gum (1.1g) from which no solid material could be obtained.

(b) A mixture of 2-nitrobenzylideneacetylacetone (415a) (2.3g, 0.01 mol), benzonitrile (1.03 ml, 0.01 mol), potassium hydrogen carbonate (1.1g, 0.011 mol), 30% aqueous hydrogen peroxide (1.3 ml, 0.011 mol) and methanol (10.0 ml) was stirred at room temperature for 18h and then at 45° for 4h. The mixture was diluted with water and extracted with chloroform to yield a gum (1.2g) whose t.l.c. in ether over silica indicated that it was a multi-component mixture, containing mainly the benzylidene starting material (415a).

(c) Repetition of (b) using 50% aqueous hydrogen peroxide again gave a multi-component mixture, consisting mainly of the benzylidene starting material (415a).

(d) 2-Nitrobenzylideneacetylacetone (415a) (1.1g, 0.005 mol) in pyridine (8.0 ml) was reacted with aqueous sodium hypochlorite (12.0 ml). The initial yellow colour rapidly darkened and the mixture was diluted with water and was extracted with chloroform. Evaporation of the washed (dilute aqueous hydrochloric acid) chloroform extract gave a dark gum (0.6g) whose ^{1}H n.m.r. spectrum {τ [$CDCl_3$] 1.76 - 2.68

(m,ArH), 5.29 (d, J 6 Hz, CH),5.84 (d, J 6 Hz, CH), 7.54 (s,Me), 7.90 (s,Me) and 8.04 (s.Me)} indicated it to be a mixture of the benzylidene starting material (415a) and cis-1-acetyl-2-(2-nitrophenyl)ethylene oxide (438).

(e) Experiment (d) was repeated using dioxan, instead of pyridine, as solvent. After stirring for 5 min the reaction mixture was diluted with water and was extracted with chloroform to give a red oil which on trituration with ether gave a light coloured solid (0.4g) whose ^{1}H n.m.r. spectrum {τ [$CDCl_3$] 1.70-2.62 (m,ArH), 5.29 (d, J 6 Hz, CH), 5.40 (d, J 2 Hz, CH), 5.83 (d, J 6 Hz, CH), 6.58 (d J 2 Hz, CH), 7.54 (s,Me), 7.74 (s,Me), 7.90 (s,Me) and 8.04 (s,Me)} indicated it to be a mixture consisting mainly of the benzylidene starting material (415a), together with cis-1-acetyl-2-(2-nitrophenyl)ethylene oxide (438) and trans-1-acetyl-2-(2-nitrophenyl)ethylene oxide (370).

Prolonging the reaction time to 1h gave the same result.

1-Cyano-2-(4-nitrophenyl)-1-phenylethylene oxide (445)

A solution of 4-nitrobenzylidenephenylacetonitrile (444) (0.6g, 0.0025 mol) in pyridine was reacted with aqueous sodium hypochlorite (6.0 ml) for 5 min at room temperature. Dilution of the reaction mixture with water and filtration afforded the epoxide (445) (0.4g, 61%), m.p. 146° (from methanol), $\nu_{max.}$ 1530 and 1360 (NO_2) cm^{-1}, τ [$CDCl_3$] 1.65-2.30 (9H,ArH) and 5.68 (1H,s,CH), m/e (rel. intensity, %) 226 (42), 212 (21), 135 (10) and 115 (100), (M 266),

Found:	C, 67.6;	H, 3.7;	N, 10.5%.
$C_{15}H_{10}N_2O_3$ requires:	C, 67.7;	H, 3.8;	N, 10.5%.

3.10 Reactions of Substituted 2-Nitrophenylethylene Oxides with Hydrogen Chloride

General Method

A solution of the epoxide (0.01 mol) in anhydrous dioxan (75 ml) was saturated with anhydrous hydrogen chloride and was left stoppered at room temperature for 80h. The reaction mixture was worked up as described below for the individual epoxides.

1-Benzoyl-1-ethoxycarbonyl-2-(2-nitrophenyl)ethylene oxide (428b)

The dioxan was evaporated under reduced pressure to give a red gum whose t.l.c. in benzene-ether (3:1) over silica indicated that it was a mixture of five components. The gum was dissolved in chloroform (A) and washed with water (5 x 10 ml). The solid which separated was collected to give 6-chloro-1,3-dihydroxy-2-phenylquinolin-4(1H)-one (368), (0.1g), m.p. 269° (decomp.) (from ethanol), identical (m.p. and i.r. spectrum) with an authentic sample.[145] The chloroform layer (A) was washed with saturated aqueous sodium hydrogen carbonate and the aqueous phase was acidified with dilute aqueous hydrochloric acid and treated with chloroform precipitating a further crop of 6-chloro-1,3-dihydroxy-2-phenylquinolin-4(1H)-one (368) (0.02g) identical (i.r. spectrum) with an authentic sample. The original chloroform extract (A) was washed with 5% w/v aqueous sodium hydroxide until the washings were colourless. Careful neutralisation of the aqueous alkaline phase with concentrated hydrochloric acid gave an insoluble solid (0.9g) m.p. 202° (decomp.) (from water)

identical (m.p. and i.r. spectrum) with an authentic sample of 5-chloroanthranilic acid prepared as described later. The aqueous acidic filtrate was buffered with sodium hydrogen carbonate and glacial acetic acid and extracted with chloroform to give benzoic acid (0.4g), identified by comparison (i.r. spectrum) with an authentic sample. The chloroform layer (A) on work-up gave a gum (0.4g) whose t.l.c. in benzene-ether (3:1) over silica indicated two main components which could not be resolved by chromatography over alumina.

1-Benzoyl-1-cyano-2-(2-nitrophenyl)ethylene oxide (428d)

Filtration of the reaction mixture gave ammonium chloride (0.1g). On standing at room temperature for 48h the dioxan filtrate deposited a solid hydrochloride which was collected and combined with a second crop obtained by evaporating the dioxan filtrate under reduced pressure (total 3.3g). The hydrochloride was stirred with water to liberate 6-chloro-1, 3-dihydroxy-2-phenylquinolin-4(1H)-one (368) (2.5g, 90%), m.p. 267°(from ethanol) (lit.,[145] 270°), identified by comparison (m.p. and i.r. spectrum) with an authentic sample.[145]

1,1-Dibenzoyl-2-(2-nitrophenyl)ethylene oxide (428e)

The dioxan was evaporated from the reaction mixture to give a red residue which was treated with chloroform and saturated aqueous sodium hydrogen carbonate. Work up of the chloroform layer gave unreacted epoxide (428e) (1.0g). The aqueous phase was acidified with dilute aqueous hydrochloric acid and the solid was collected (0.7g) to afford 6-chloro-1,3-dihydroxy-2-phenylquinolin-4(1H)-one (368), m.p. 268° (from ethanol), identical (m.p. and i.r. spectrum) with an authentic sample.[145]

The acidic aqueous phase was buffered with sodium hydrogen carbonate and glacial acetic acid and was extracted with chloroform to give benzoic acid (0.1g), identified by comparison of its i.r. spectrum with that of an authentic sample.

1-Cyano-2-(2-nitrophenyl)-1-phenylethylene oxide (430b)

The reaction mixture was evaporated under reduced pressure to give an orange oil whose t.l.c. in benzene-ether (1:1) showed the presence of five components. A solution of the oil in chloroform was washed with saturated aqueous sodium hydrogen carbonate until the washings were almost colourless. The aqueous phase was acidified with concentrated hydrochloric acid and yellow crystals of α-(2-nitrobenzoyl)phenylacetonitrile (461) (0.2g) were collected, m.p. 148° (from ethanol), $\nu_{max.}$ 3050, 2700 (OH), 2250 (CN), 1640 (CO) and 1540 and 1350 (NO_2) cm^{-1}, m/e (rel. intensity, %) 266 (4), 150 (100) and 116 (44), (M 266),

Found: C, 67.7; H, 3.7; N, 10.7%.

Calculated for $C_{15}H_{10}N_2O_3$: C, 67.7; H, 3.8; N, 10.5%.

Extraction of the aqueous filtrate with chloroform gave no further material. The original chloroform phase gave a yellow gum (2.7g) which was chromatographed over silica. Elution with toluene-ether (20:1) gave 2-nitrobenzylidenephenylacetonitrile (415b) (0.02g) identified by comparison (i.r. spectrum) with an authentic sample. Elution with toluene-ether (10:1) afforded the chlorohydrin (462) (1.9g), m.p. 114° (from light petroleum-benzene), $\nu_{max.}$ 3500 (OH) and 1540 and 1370 (NO_2) cm^{-1}, τ [$CDCl_3$] 1.90 (1H, dd, J_{ortho} 9 Hz, J_{meta} 2 Hz, ArH), 2.50 (8H,m,ArH), 3.67 (1H, d, J 4 Hz,

CH), and 6.36 (1H, J 4Hz, OH). The signal at τ 3.67 collapsed to a singlet and that at τ 6.36 disappeared when the sample was shaken with D_2O.

Found: C,59.5; H,3.7; N,9.1%; M^+304/302.
$C_{15}H_{11}ClN_2O_3$ requires: C,59.5; H,3.6; N,9.3%; M 304/302.

Further elution with solvents of increasing polarity yielded no more material.

A solution of the chlorohydrin (462) (0.3g, 0.001 mol) in absolute ethanol (10.0 ml) was heated under reflux for 3 min with a solution of sodium (0.23g, 0.01 mol) in absolute ethanol (2.0 ml). The cooled reaction mixture was evaporated under reduced pressure and the residue was treated with water and chloroform. Work-up of the chloroform extract gave the epoxide (430b) (0.2g), m.p. 124°, identical (m.p. and i.r. spectrum) with an authentic sample. The alkaline aqueous phase was carefully acidified with concentrated hydrochloric acid and was then extracted with chloroform to give, on trituration with ether, α-(2-nitrobenzoyl)phenylacetonitrile (461) (0.03g) identical (m.p. and i.r. spectrum) to a sample obtained previously.

1,1-Diethoxycarbonyl-2-(2-nitrophenyl)ethylene oxide (429a)

The dioxan reaction mixture was evaporated under reduced pressure to give a gum whose t.l.c. in benzene-ether (2:1) over silica showed it to contain at least six components. The gum was chromatographed over silica, the polarity of the eluting solvent being increased from light petroleum through toluene, but gave no definable products. Elution with toluene-ether (20:3) gave a gummy solid (0.6g), $\nu_{max.}$ 3450 (OH),

1750 and 1720 (CO) cm^{-1}, whose structure was not elucidated.

1-Cyano-1-ethoxycarbonyl-2-(2-nitrophenyl)ethylene oxide (429c)

Evaporation of the dioxan reaction mixture under reduced pressure gave a yellow gum whose t.l.c. in benzene-ether (2:1) over silica showed it to be a mixture of four components. A solution of the gum in chloroform was washed with water. The aqueous phase was neutralised with sodium acetate and was extracted with chloroform to give a negligible amount of a gum. The chloroform layer was washed with saturated aqueous sodium hydrogen carbonate. Neutralisation of the sodium hydrogen carbonate washings with dilute aqueous hydrochloric acid and extraction with chloroform gave a negligible amount of a gum. The original chloroform layer was evaporated to yield a gum (2.0g) which was chromatographed over silica. Elution with toluene-ether (95:5) gave unreacted epoxide (429c) (0.5g), identical (m.p. and i.r. spectrum) with an authentic sample. Elution with toluene-ether (70:30) gave 5-chloro-3-oxamoyl-2,1-benzisoxazole (478) (0.15g), m.p. 173° (from benzene), $\nu_{max.}$ 3400, 3200br (NH_2), and 1710 and 1670 (CO) cm^{-1}, τ [$(CD_3)_2CO$] 1.50br (1H,s,NH), 1.72br (1H,s,NH), 1.84 (1H, d, J_{meta} 2 Hz, ArH), 2.01 (1H, d, J_{ortho} 9 Hz, ArH) and 2.45 (1H, dd, J_{ortho} 9 Hz, J_{meta} 2 Hz, ArH),

Found: C,47.3; H,2.2; N,12.3%; M^+ 226/224.

$C_9H_5ClN_2O_3$ requires: C,48.1; H,2.2; N,12.5%; M 226/224.

Further elution with toluene-ether (55:45) afforded a sand-coloured solid (0.6g) identified as ethyl α-(5-chloro-2,1-benzisoxazol-3-yl)-α-hydroxymalonamate (477) m.p. 113° (from

ethanol-light petroleum), $\nu_{max.}$ 3450, 3200 (NH_2) and 1730, 1710 (CO) and 1680 (NH def.) cm^{-1}, τ [$(CD_3)_2CO$] 2.14 (1H, d, J_{meta} 2 Hz, ArH), 2.39 (1H, d, J_{ortho} 9 Hz, ArH), 2.50br (2H,NH_2), 2.70 (1H, dd, J_{ortho} 9 Hz, J_{meta} 2 Hz, ArH), 3.16br (1H,s,OH), 5.59 (2H, q, J 7 Hz, CH_2) and 8.75 (3H, t, J 7 Hz, Me).

Found: C,48.0; H,3.7; N,9.5%; M^+ 300/298.

$C_{12}H_{11}ClN_2O_5$ requires: C,48.3; H,3.7; N,9.4%; M 300/298.

Further elution with toluene-ether (50:50) yielded 1-carbamoyl-1-ethoxycarbonyl-2-(2-nitrophenyl)ethylene oxide (429d) (0.02g) identified by comparison (i.r. spectrum) with an authentic sample.

1-Carbamoyl-1-ethoxycarbonyl-2-(2-nitrophenyl)ethylene oxide (429d)

Filtration of the dioxan reaction mixture gave ammonium chloride (0.25g). The filtrate was evaporated under reduced pressure to give a viscous red gum whose t.l.c. in benzene-ether (1:2) over silica indicated a mixture of seven components. A solution of this gum in chloroform was washed with saturated aqueous sodium hydrogen carbonate. No material was obtained by extracting the aqueous phase with chloroform. The original chloroform phase was evaporated to give a red gum (2.0g) which was chromatographed over silica. Elution with toluene-ether (100:35) gave 5-chloro-3-oxamoyl-2,1-benzisoxazole (478) (0.5g) identical (m.p. and i.r. spectrum) with a sample obtained previously. Further elution gave gums (total 1.1g) whose t.l.c. showed them to be unresolvable mixtures.

The Oxidation of Ethyl α-(5-Chloro-2,1-benzisoxazol-3-yl)-α-hydroxymalonamate (477) with Chromium Trioxide

The anthranil (477) (0.1g) dissolved in 70% v/v aqueous acetic acid (3.0 ml) was heated on a steam bath for 1h with chromium trioxide (0.2g). The mixture was evaporated under reduced pressure giving a green residue which was treated with water. The insoluble green solid (0.1g) was dissolved in the minimum of saturated aqueous sodium hydrogen carbonate, filtered to remove insoluble material, and the filtrate was carefully acidified with concentrated hydrochloric acid to give 4,4'-dichloroazoxybenzene-2,2'-dicarboxylic acid (0.02g), m.p. 260° (decomp.) (from glacial acetic acid) (lit.,[49] 264°), identified by comparison (m.p. and i.r. spectrum) with an authentic sample.[49]

The Attempted Acetylation of Ethyl α-(5-Chloro-2,1-benzisoxazol-3-yl)-α-hydroxymalonamate (477)

The anthranil (477) (0.02g) was heated at 100° for 20 min with acetic anhydride (2 drops). The reaction mixture was cooled and scratched to give unreacted anthranil (477) (0.02g), identical (i.r. spectrum) to an authentic sample.

The Reaction of Ethyl α-(5-Chloro-2,1-benzisoxazol-3-yl)-α-hydroxymalonamate (477) with Aqueous Alkali

The anthranil (477) (0.05g) was treated with 10% w/v aqueous sodium hydroxide (0.5ml) giving a magenta coloured solution from which a solid separated on scratching. A little more aqueous sodium hydroxide was added giving a red solution whose colour faded to orange over 5 min. The solution was acidified with concentrated hydrochloric acid and was extracted with

chloroform to give a solid (0.02g) whose t.l.c. in benzene-ether (1:1) over silica showed it to be an unresolvable mixture of three components.

The Reduction of Ethyl α-(5-Chloro-2,1-benzisoxazol-3-yl)-α-hydroxymalonamate (477)

The anthranil (477) (0.3g, 0.001 mol) was heated under reflux in 70% v/v aqueous ethanol (25 ml) with sodium dithionite (0.3g) for 1h. A second portion of sodium dithionite (0.3g) was added and heating was continued for a further 1h. Filtration of the cooled reaction mixture gave a solid which was combined with a second crop obtained by leaching the evaporated mother liquors with ethanol giving 6-chloro-2,3-dihydroxyquinolin-4(1H)-one (483) (0.2g), m.p. 298° (from aqueous dimethylformamide) $\nu_{max.}$ 3350br, 3150br, 2700 (OH) and 1640 (CO) cm^{-1},

Found: C,49.9; H,3.0; N,6.4%; M^+ 211/213.

$C_9H_6ClNO_3$ requires: C,51.1; H,2.8; N,6.6%; M 211/213.

This product gave a deep blue colour when its solution in ethanol was treated with a solution of iron(III) chloride in ethanol.

The Attempted Hydrogenolysis of 6-Chloro-2,3-dihydroxyquinolin-4(1H)-one (483)

The chloroquinolinone (483) (0.1g, 0.0005 mol) in ethanol (20 ml) was hydrogenated at room temperature and atmospheric pressure over 10% palladium-on-charcoal (0.01g). Filtration and evaporation of the ethanol gave only unreacted starting material (0.08g).

The Reaction of 5-Chloro-3-oxamoyl-2,1-benzisoxazole (478) with Aqueous Alkali

The anthranil (478) (0.1g) was treated with 10% w/v aqueous sodium hydroxide (1.0 ml) and the anthranil started to dissolve, then a solid separated. The mixture was heated at 100° for 5 min and was cooled and acidified with concentrated hydrochloric acid to give a light coloured solid (0.03g), m.p. 200° (from water), identified as 5-chloroanthranilic acid (455) by comparison of its i.r. spectrum with that of an authentic sample, prepared as described later.

The Reduction of 5-Chloro-3-oxamoyl-2,1-benzisoxazole (478)

The anthranil (478) (0.2g, 0.001 mol) in 70% v/v aqueous ethanol (30 ml) was heated under reflux for 2h as above with two portions (0.2g) of sodium dithionite. The cooled reaction mixture was evaporated under reduced pressure and the residue was treated with water and chloroform. Work up of the chloroform extract gave 1-(2-amino-5-chlorophenyl)-1-hydroxypyruvamide (493) (0.02g), m.p. 119-122°, $\nu_{max.}$ 3450, 3350 (NH), 3200br (OH), 1680, 1650 (CO), 1620 and 1600 (NH def.) cm^{-1}, M^+ 230/228 (M 230/228). The aqueous phase was evaporated under reduced pressure to give a residue which was heated under reflux with ethanol and filtered hot. Evaporation of the ethanol extract gave a yellow gum from which no identifiable material could be obtained.

5-Chloroanthranilic acid (455) was prepared[192] by chlorinating anthranilic acid with sulphuryl chloride (51%), m.p. 202° (from water) (lit.,[192] 204°).

3.11 The Reaction of 1-Benzoyl-2-(2-nitrophenyl)cyclopropane with Hydrogen Chloride

Trimethyloxosulphonium iodide (502) was prepared (49%) as described by Kuhn and Trischmann.[193]

1-Benzoyl-2-(2-nitrophenyl)cyclopropane (504)

Anhydrous dimethylsulphoxide (10.0 ml) was added to a mixture of sodium hydride (0.29g, 0.012 mol) and trimethyloxosulphonium iodide (2.42g, 0.011 mol). The brisk evolution of hydrogen ceased after 15 min giving a clear solution. To this was added a solution of 2-nitrobenzylideneacetophenone (411a) (2.5g, 0.01 mol) in anhydrous dimethylsulphoxide (25.0 ml) and the mixture was stirred at 50° for 1h and was then diluted with water (300 ml). Extraction with chloroform and evaporation of the extract afforded the cyclopropane (504) as a red oil (1.6g, 62%), $\nu_{max.}$ 1670 (CO), 1530 and 1360 (NO_2) cm^{-1}, τ [$CDCl_3$] 1.98-2.72 (8H,m,ArH), 6.76-7.22 (2H,m,CH) and 8.04-8.56 (2H,m,CH), M^+ 267 (M 267), which was used without further purification.

Reaction of 1-Benzoyl-2-(2-nitrophenyl)cyclopropane (504) with Hydrogen Chloride

A solution of the cyclopropane (504) (1.3g, 0.005 mol) in anhydrous ether (10.0 ml) was saturated with anhydrous hydrogen chloride and was left at room temperature for 20h. The ether was evaporated and the gummy residue was triturated with ether to yield 1-benzoyl-1-chloro-3-(2-nitrophenyl)propane (505) (1.0g, 66%), m.p. 84° (from light petroleum), $\nu_{max.}$ 1680 (CO), 1540 and 1360 (NO_2) cm^{-1},

τ [$CDCl_3$] 2.00-2.68 (9H,m,ArH), 3.34 (1H, dd, J 5 and 6 Hz), 6.76 (2H,m,CH) and 7.45 (2H,m,CH),

Found:	C, 62.9;	H, 4.6;	N, 4.5%.
$C_{16}H_{14}ClNO_3$ requires:	C, 63.3;	H, 4.6;	N, 4.6%.

To a solution of the chloropropane (505) (0.01g) in glacial acetic acid (ca. 1 ml) was added potassium iodide (0.01g). Immediately a straw colour developed which gave a deep blue colour when treated with a freshly prepared starch solution.

Reaction of 1-Benzoyl-1-chloro-3-(2-nitrophenyl)propane (505) with Sodium Ethoxide

1-Benzoyl-1-chloro-3-(2-nitrophenyl)propane (505) (0.3g, 0.001 mol) dissolved in absolute ethanol (20 ml) was heated under reflux for 0.5h with a solution of sodium (0.1g, 0.004 mol) in absolute ethanol (8.0 ml). The mixture was evaporated under reduced pressure and the residue was treated with water and chloroform. The chloroform extract gave 1-benzoyl-2-(2-nitrophenyl)cyclopropane (504) (0.2g, 75%) identical (i.r. spectrum) with an authentic sample. Chloroform extraction of the aqueous phase gave no further material.

Appendix

General Experimental Details

Infrared spectra were recorded for nujol mulls or liquid films on a Pye Unicam S.P.200 Spectrophotometer. Absorption bands were sharp unless specified (br) as broad.

Unless otherwise stated, ultraviolet and visible spectra were recorded for ethanol solutions on a Pye Unicam S.P.600 Spectrophotometer.

Mass spectra were recorded at 70 eV on an A.E.I. MS 902 Spectrometer.

Nuclear magnetic resonance spectra (^{1}H n.m.r.) were recorded at 100 MHz on a Varian HA 100 instrument using tetramethylsilane as internal standard. Signals were sharp unless specified (br) as broad; s = singlet, d = doublet, dd = double doublet, t = triplet, q = quartet, m = multiplet.

Elemental analyses were carried out by Alfred Bernhardt, West Germany, The National Physical Laboratory, Teddington and by Mr. B. Clark and Mr. J. Grunbaum, Department of Chemistry, University of Edinburgh. Melting points of analytical samples were determined on a Kofler-block and are uncorrected.

Wet-column chromatography was carried out over Spence type H alumina or Fison's (100-200 mesh) silica gel.

Dry-column chromatography was carried out over alumina (Spence type H, activity III).

Thin-layer chromatography (t.l.c.) was carried out over silica [Merck Keiselgel G.F.$_{254}$ (Type 60)] or alumina [Merck G.F.$_{254}$ (Type 601E)].

High speed liquid chromatography was carried out over alumina (Spherisorb A 20 X, 20 μm average diameter and 200 m^2/g surface area).

Solvents were of technical grade and, unless otherwise stated, light petroleum had b.p. 60-80°.

Organic extracts were dried ($MgSO_4$) prior to evaporation under reduced pressure.

The aqueous sodium hypochlorite used in the epoxidation reactions contained 6% available chlorine and was prepared by diluting the commercially available aqueous solution with an equal volume of water.

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Intramolecular Nucleophilic Aromatic Substitution Reactions Involving the Novel Displacement of Hydride Ion by Cyanobenzyl Carbanions

By D. W. Bayne, G. Tennant,* and (in part) T. W. M. Spence
(*Department of Chemistry, Universiry of Edinburgh, West Mains Road, Edinburgh* EH9 3JJ)

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Intramolecular Nucleophilic Aromatic Substitution Reactions Involving the Novel Displacement of Hydride Ion by Cyanobenzyl Carbanions

By D. W. BAYNE, G. TENNANT,* and (in part) T. W. M. SPENCE
(*Department of Chemistry, University of Edinburgh, West Mains Road, Edinburgh* EH9 3JJ)

Summary α-(*N*-Substituted-*N*-3,5-dinitrobenzoylamino)-, α-(*N*-substituted-*N*-2-chloro-3,5-dinitrobenzoylamino)-, and α-(*N*-substituted-*N*-3-nitrobenzoylamino)phenylacetonitriles (1) and (2) undergo base-catalysed cyclisation with displacement of hydride ion or chloride ion to afford the corresponding isoindolin-1-ones (3), (4), and (5).

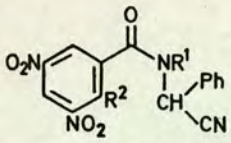
HYDRIDE ion displacement[1] is comparatively rare in nucleophilic aromatic substitution reactions. Intramolecular processes of this type do not appear to have been reported hitherto. Recently, we described[2] examples of the intramolecular nucleophilic displacement of aromatic nitro-groups by carbanions. We now report cyclisation reactions of nitrobenzene derivatives involving the analogous displacement of hydride ion by cyanobenzyl carbanions.†

Heating compound (1a) under reflux with aqueous 1N sodium carbonate gave a mixture, chromatography of which afforded the compound (3a) (20%), m.p. 228°, which showed characteristic[3] i.r. carbonyl absorption at 1720 cm^{-1} and ^1H n.m.r. absorption at τ ($CF_3 \cdot CO_2H$) 0·56 [1H, d, H(5) or H(7)] and 0·73 [1H, d, H(7) or H(5)], and was identical with the dinitroisoindolinone prepared (95%) by cyclising[2] (1d) in hot aqueous ethanolic sodium acetate.

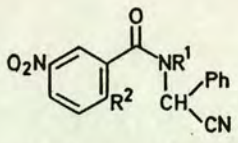
The formation of compound (3a) from (1a) is readily explained in terms of the formal intramolecular displacement of hydride ion by cyanobenzyl carbanion generated in the side-chain (*cf.* Scheme). Concomitant reduction of the substrate and/or product by the liberated hydride ion [or by the intermediate adduct (7)] then accounts for the low yield of (3a) and the formation of by-products. In support of these contentions, compound (3a), was obtained in quantitative yield when the sodium acetate catalysed cyclisation of (1a) was carried out in the presence of a mild oxidising agent such as *p*-benzoquinone to scaveng ethe hydride ion formed [or alternatively to oxidise the intermediate (7) into (3a)]. Similar cyclisation of the amides (1b and c) in the presence of *p*-benzoquinone gave quantitative yields of the compounds (3b), m.p. 179°, and (3c), m.p. 134° which were identical with the isoindolinones

† Satisfactory analyses were obtained for all new compounds.

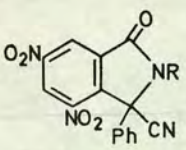
formed by the sodium acetate catalysed cyclisation of compounds (1e) and (1f).



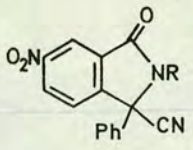
(1) R^1 R^2
a; Ph H
b; CH_2Ph H
c; Me H
d; Ph Cl
e; CH_2Ph Cl
f; Me Cl



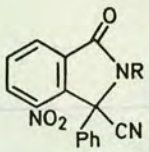
(2) R^1 R^2
a; Ph H
b; CH_2Ph H
c; CH_2Ph Cl



(3) R
a; Ph
b; CH_2Ph
c; Me



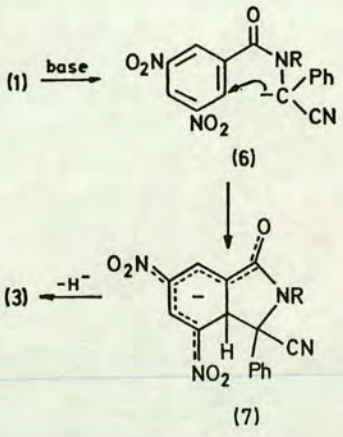
(4)



(5)

R
a; Ph
b; CH_2Ph

A single nitro-group provides sufficient activation for cyclisation with hydride displacement. Thus, heating the (2a) under reflux with aqueous ethanolic sodium carbonate gave the known[2] compound (4a) (30%), m.p. 225°, τ (CF_3·CO_2H) 1·00 [1H, d, H(7)], 1·26 [1H, q, H(5)], and 2·19 [1H, d, H(4)], together with the compound (5a) (2%), m.p. 214°, τ (CF_3·CO_2H) 1·25 [1H, dd, H(5) or H(7)], 1·42 [1H, dd, [H(7) or H(5)], and 1·87 [1H, t, H(6)], demonstrating competing nucleophilic attack *ortho* and *para* to the nitro-group. Similar cyclisation of (2b) in the presence of *p*-benzoquinone again occurred in higher yield to afford a readily separated mixture of the isomeric compounds (4b) (62%), m.p. 158° [identical with an authentic sample prepared (92%) by cyclising (2c) in hot aqueous ethanolic sodium carbonate] and (5b) (8%), m.p. 148°.



SCHEME

The ease of hydride displacement by the side-chain carbanion in the amides (1a—c) and (2a and b) is remarkable and may be due at least in part to the favourable steric situation. In contrast, the intermolecular substitution[3] of nitrobenzenes by cyanobenzyl carbanions appears to require more extreme conditions and yields products (quinone oximes, nitrones, azoxy-compounds) derived from nitrosobenzene intermediates formed by the predominant expulsion of hydroxide ion (as opposed to hydride ion) from initial carbanion adducts [*cf.* (7)].

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